



FLS Bone Health ECHO® TeleECHO Clinic

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By participating in this clinic you are consenting to be recorded.

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- Please type in your name, location, and email address in the chat.

Some helpful tips:

- Please mute your microphone when not speaking
- Position webcam effectively
- Communicate clearly during clinic:
 - Speak clearly
 - Use chat function

Project ECHO's goal is to protect patient privacy

To help Project ECHO accomplish that goal, please only display or say information that doesn't identify a patient or that cannot be linked to a patient.

References:

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Common HIPAA Identifier Slip-Ups and Easy Ways to Protect Patient Privacy

- 1st – **Names:** Please do not refer to a patient's *first/middle/last name* or use any *initials*, etc. Instead please use the *ECHO ID*.
- 2nd – **Locations:** Please do not identify a patient's *county, city or town*. Instead please use only the patient's *state* if you must or the *ECHO ID*.
- 3rd – **Dates:** Please do not use any dates (like *birthdates*, etc.) that are linked to a patient. Instead please use only the patient's *age* (unless > 89)
- 4th – **Employment:** Please do not identify a patient's *employer*, work *location* or *occupation*. Instead please use the *ECHO ID*.
- 5th – **Other Common Identifiers:** Do not identify patient's *family* members, *friends, co-workers, numbers, e-mails*, etc.

HYPERPARATHYROIDISM

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Disclosures

- Speaker (Honorarium): Shire Pharmaceuticals/Takeda, Alexion
- Consultant (Honorarium): Shire Pharmaceuticals/Takeda, Radius Pharmaceuticals
- Off-label use of estrogen, raloxifene and alendronate

Learning objectives

- Recognize the complications of primary hyperparathyroidism.
- Identify patients with primary hyperparathyroidism who are candidates for parathyroid surgery.
- Medically manage patients with primary hyperparathyroidism.

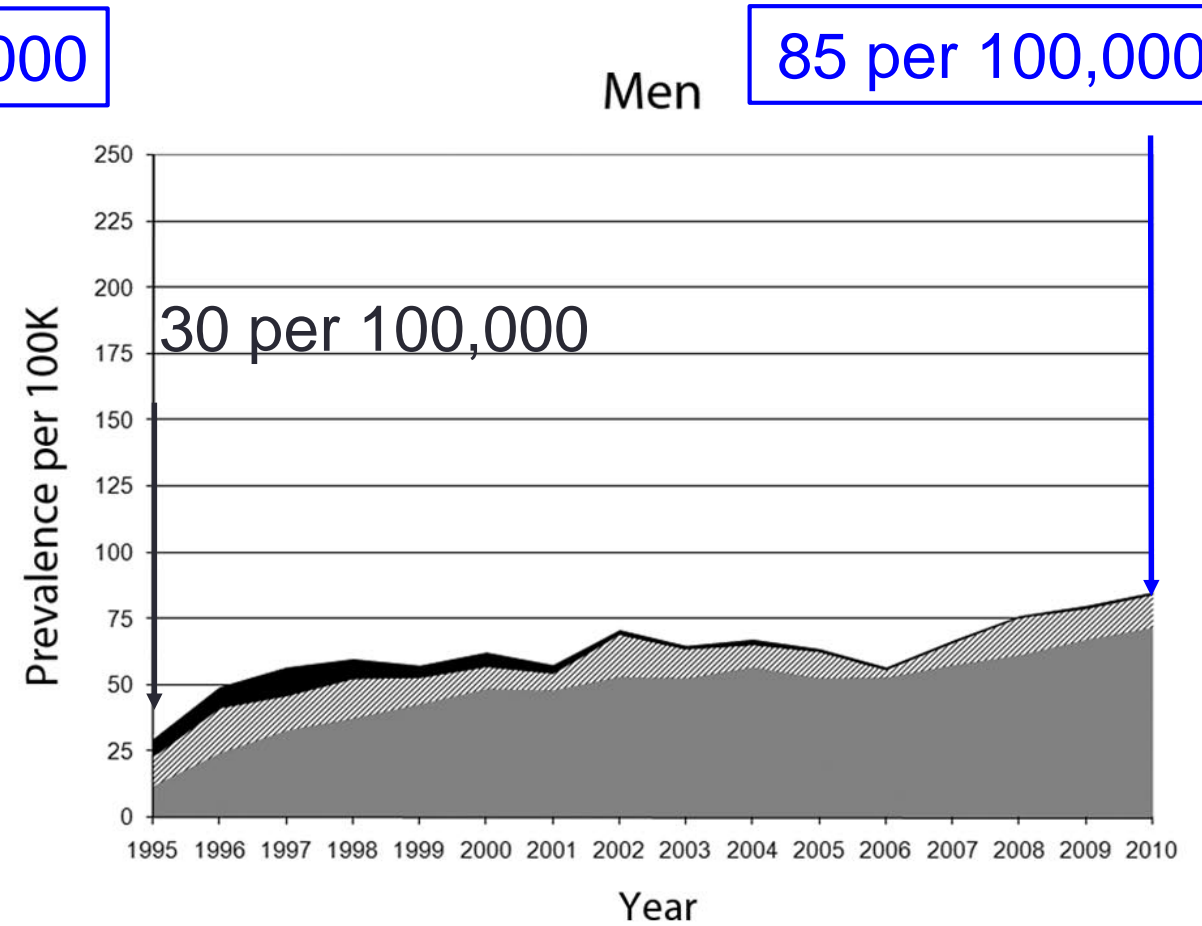
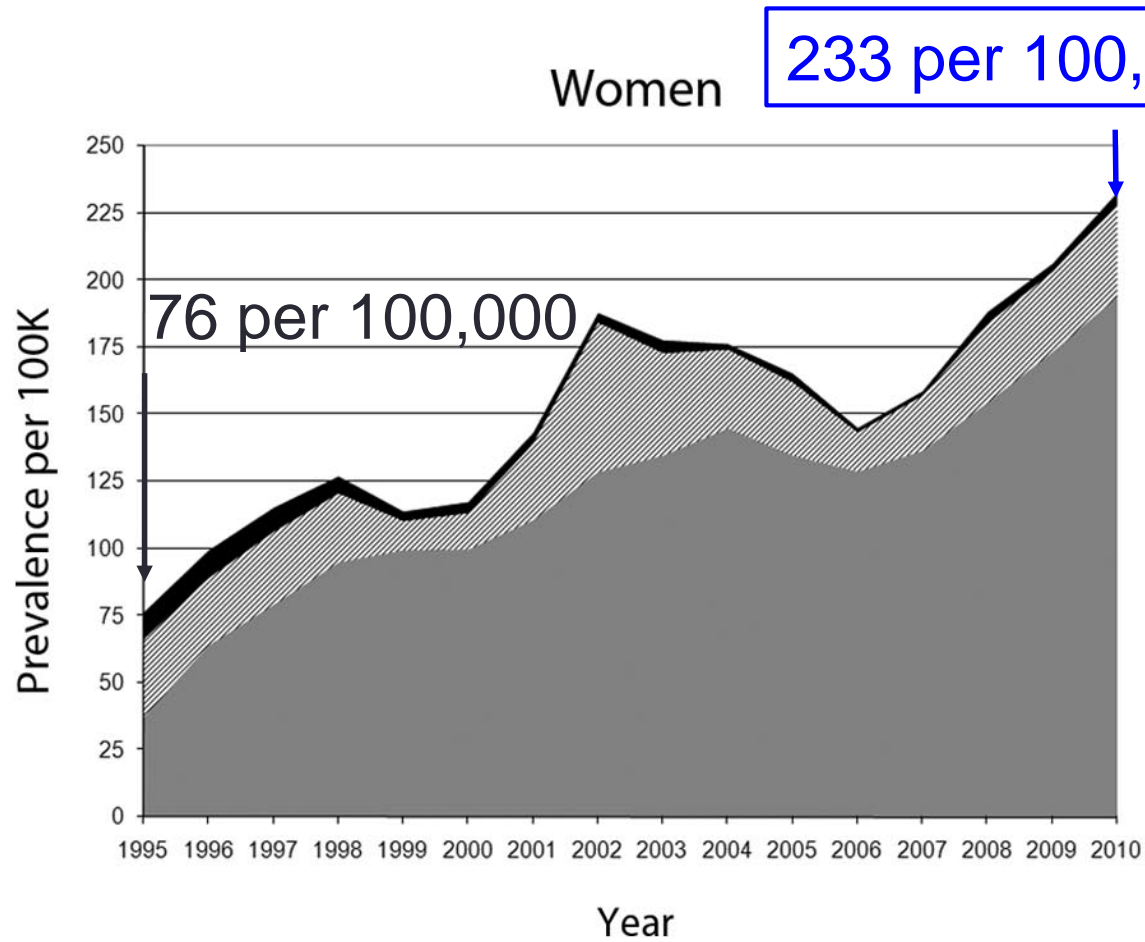
Outline

- Introduction
- Clinical presentation
- Guidelines
 - Screening and management
 - Bones
 - Kidney
 - Normocalcemic primary hyperparathyroidism
 - Medical therapy
 - Surgery

Primary hyperparathyroidism is common

- Parathyroid hormone (PTH) is made by the (usually) four parathyroid glands that sit on top of the thyroid
- Primary hyperparathyroidism (PHPT) is a disorder traditionally characterized by elevated levels of PTH and hypercalcemia
- PHPT is one of the most common endocrine disorders
 - Estimated prevalence 0.1-1% in postmenopausal women
 - Prevalence is about 3 times greater in women than men
 - More common with increasing age
 - **PHPT is a common secondary cause of osteoporosis**

The prevalence of PHPT in the US has tripled



Phenotypes of PHPT

Before 1970:

A disease of bones, stones, groans, and moans

The early clinical picture of PHPT

1918



The early clinical picture of PHPT

1918



1926



Phenotypes of PHPT

Before 1970:

A disease of bones, stones, groans, and moans

After 1970:

A disease with primarily biochemical and densitometric signatures

The modern clinical profile of PHPT

	Cope ¹ 1930-1965	Mallette ² 1965-1974	Silverberg ³ 1984-1999	Walker ⁴ 2000-2014
Nephrolithiasis	57%	37%	17%	19%
Hypercalciuria	NR	40%	39%	17%
Overt skeletal disease	23%	14%	1.4%	0%
Asymptomatic	0.6%	22%	82%	81%

¹Cope O. N Engl J Med 1966;274:1174-82; ²Mallette LE, et al. Medicine (Baltimore) 1974;53:127-46; ³Silverberg SJ, et al. N Engl J Med 1999;341:1249-55; ⁴Walker MD, et al. Osteoporos Int 2015; 26:2837-43

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*More common if imaging performed for screening

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- 96 patients with PHPT without known history of nephrolithiasis
 - Occult urolithiasis was detected in 21% of patients

Tay YD, et al. Endocr Res 2018 May;43:106-115

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The biochemical signature of PHPT in the modern era

Index	1984-1991 N=121	2000-2014 N=100	p value	Normal range
Calcium (mg/dL)	10.6 ± 0.6	10.7 ± 0.6	0.14	8.4-10.2
PTH (pg/mL)	127 ± 69	85 ± 48	<0.0001	10-65
25-hydroxyvitamin D (ng/mL)	23 ± 10	29 ± 10	<0.0001	30-100
1,25-dihydroxyvitamin D (pg/mL)	57 ± 20	69 ± 24	0.002	15-60
Urinary calcium excretion (mg)	229 ± 119	250 ± 144	0.28	100-300

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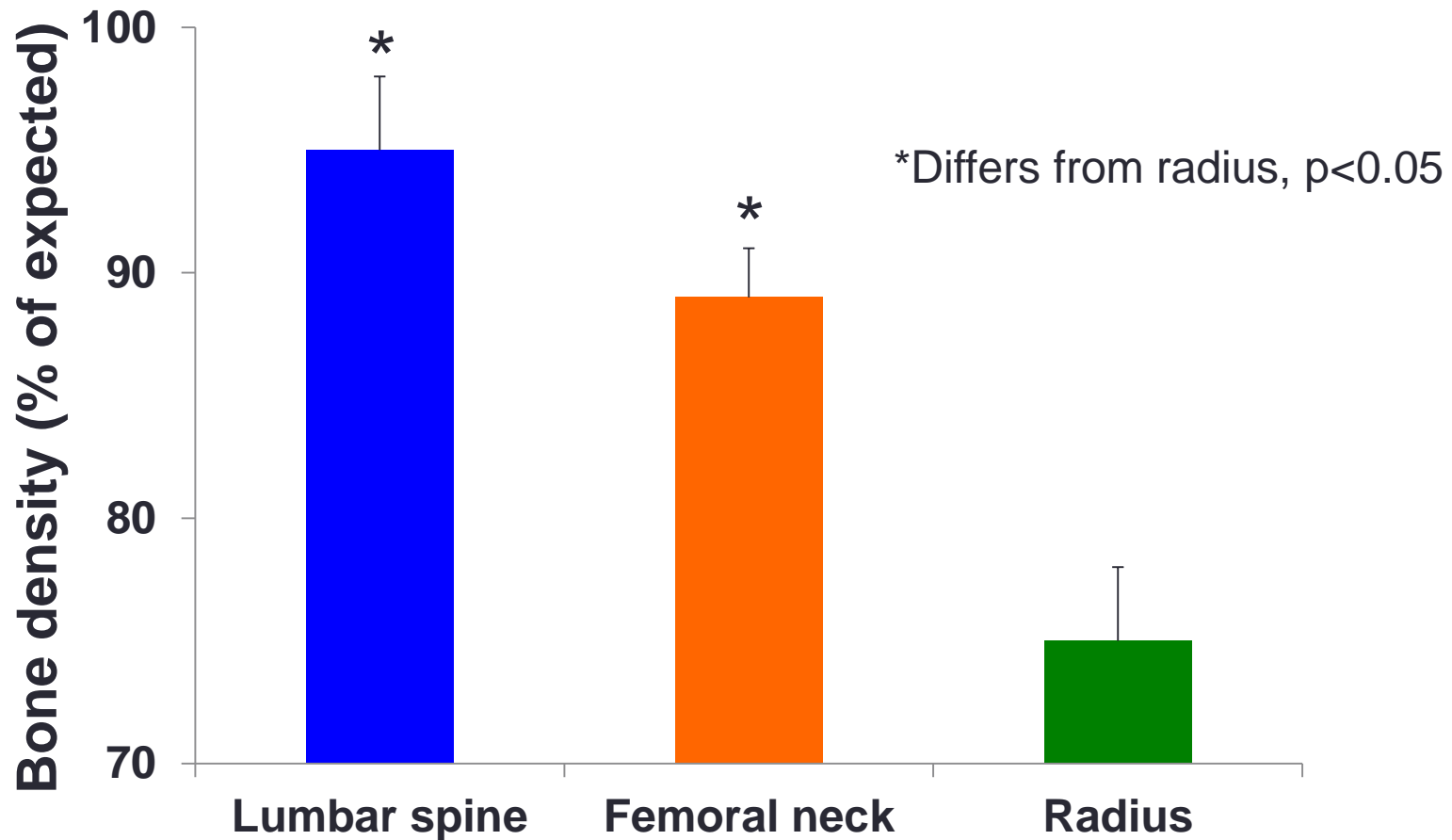
None of the patients in the prior cohort were taking vitamin D supplements compared to 64% in the new cohort (median 800 IU daily)

The biochemical signature of PHPT in the modern era

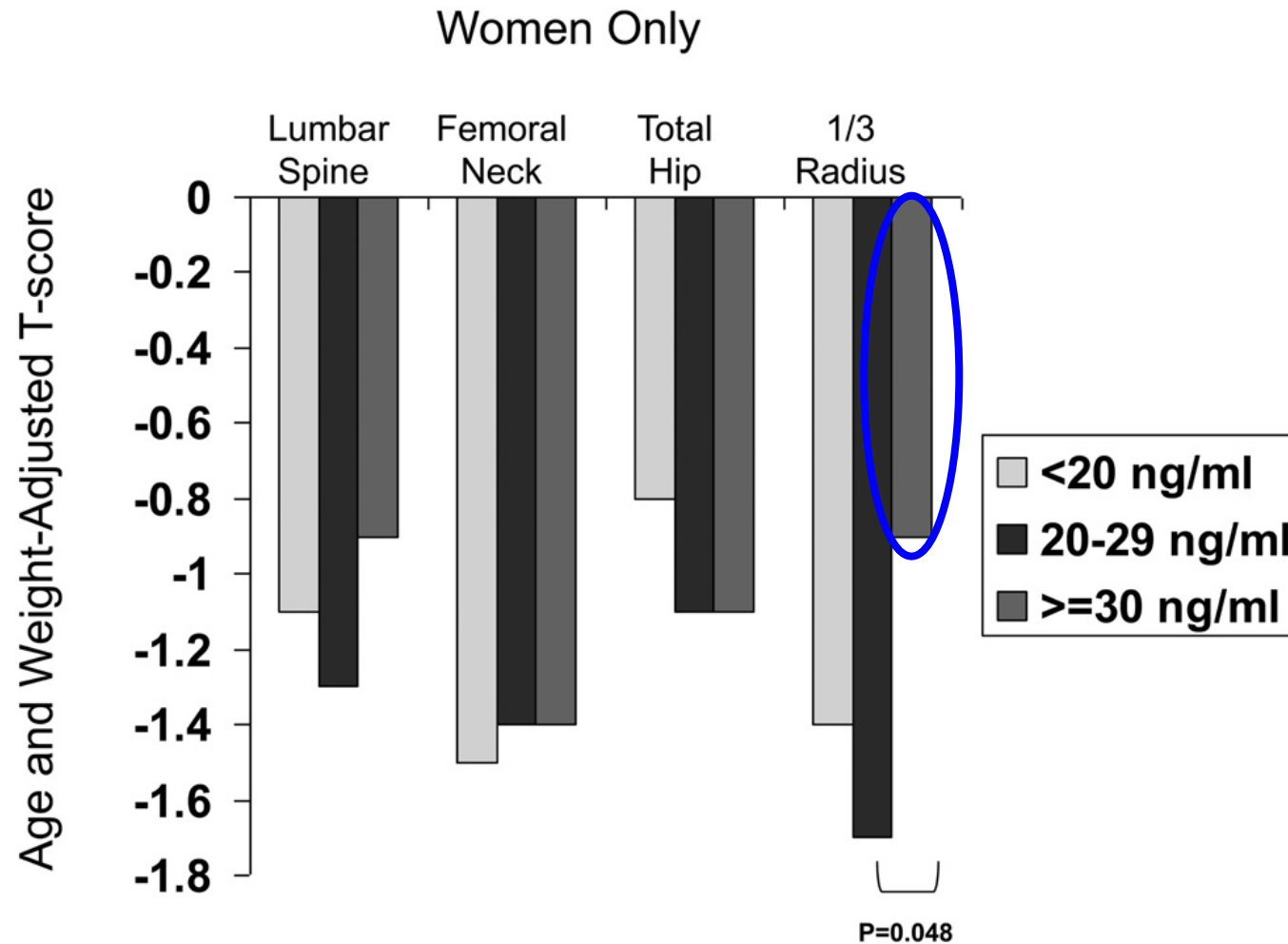
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Primary hyperparathyroidism can be diagnosed with an “inappropriately normal” PTH concentration (>20 pg/mL)

The densitometric signature of PHPT in the modern era



The densitometric signature of PHPT in the modern era -2-



Management of **asymptomatic** PHPT

- Who needs surgery?
- Who doesn't need surgery?

Even though patients may not meet any specific criteria for surgery, parathyroidectomy is not inappropriate, as long as there are no medical contraindications

Management of asymptomatic PHPT

- Who needs surgery?
- Who doesn't need surgery?

- First International Workshop, 1990
- Second International Workshop, 2002
- Third International Workshop, 2008
- Fourth International Workshop, 2013

- American Association of Endocrine Surgeons, 2016

Guidelines overview

- Biochemical presentation
- Diagnostics
- Clinical presentations
- Natural history
- Densitometric features
- Other skeletal features
- Non-traditional features
- Pharmacological approaches
- Localization and surgical approaches

Bilezikian JP, et al. J Clin Endocrinol Metab 2014;3561-9
Eastell R, et al, J Clin Endocrinol Metab 2014;99:3570-9
Silverberg SJ, et al. J Clin Endocrinol Metab 2014;99:3580-94
Udelsman R, et al. J Clin Endocrinol Metab 2014;99:3595-606
Marcocci C, et al. J Clin Endocrinol Metab 2014;99:3607-18

Wilhelm SM, et al. JAMA Surg 2016;151:959-68

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Surgical guidelines for asymptomatic PHPT

Index	Third workshop (2008)	Fourth workshop (2013)
Age	<50 years	<50 years
Serum calcium	>1.0 mg/dL above normal	>1.0 mg/dL above normal

Recommendation 3-2: Parathyroidectomy is indicated when the serum calcium level is greater than 1 mg/dL above normal, regardless of whether objective symptoms are present or absent (strong recommendation; low-quality evidence)

Recommendation 3-5: Parathyroidectomy is indicated when PHPT is diagnosed at 50 years or younger regardless of whether objective or subjective features are present or absent (strong recommendation; moderate-quality evidence)

Fracture risk in PHPT

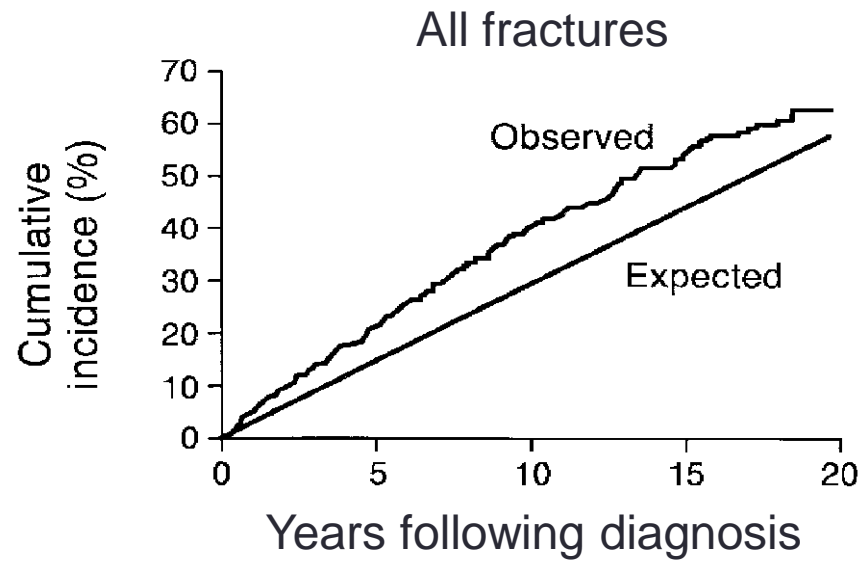
- Bone density and bone biopsy data show decreased cortical bone but preservation of the trabecular skeleton¹⁻³
- Fracture risk may be expected to be
 - ↓ at vertebral sites
 - ↑ at nonvertebral sites

¹Silverberg SJ et al. J Bone Miner Res 1989;4:283-91

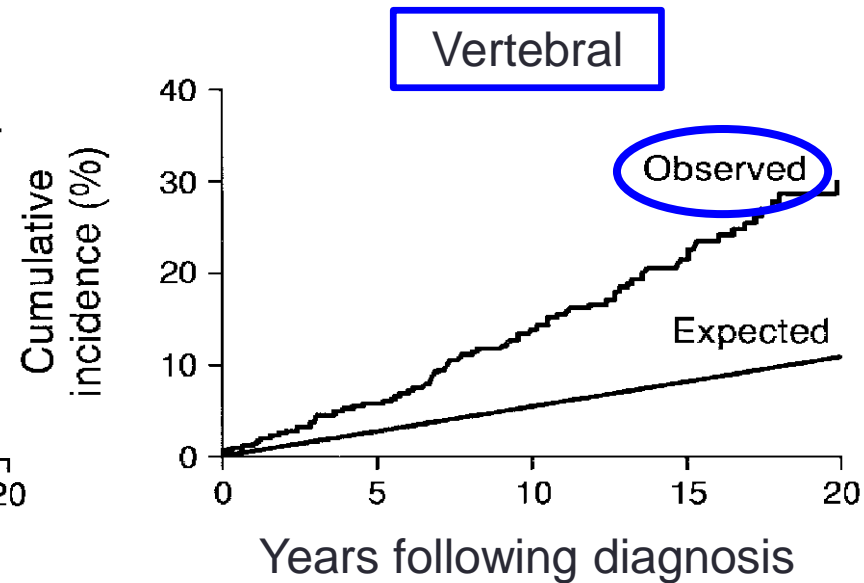
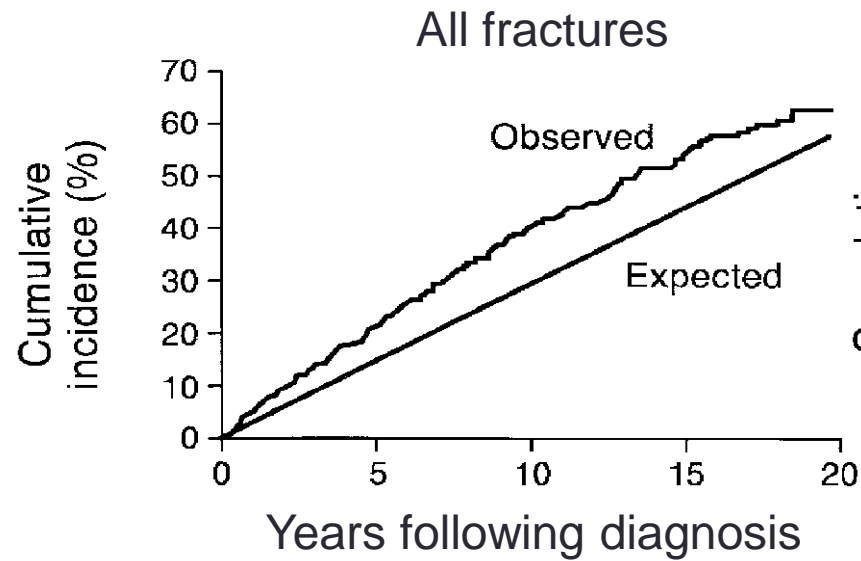
²Parisien M, et al. J Clin Endocrinol Metab 1990;70:930-8

³Dempster DW, et al. Bone 2007;41:19-24

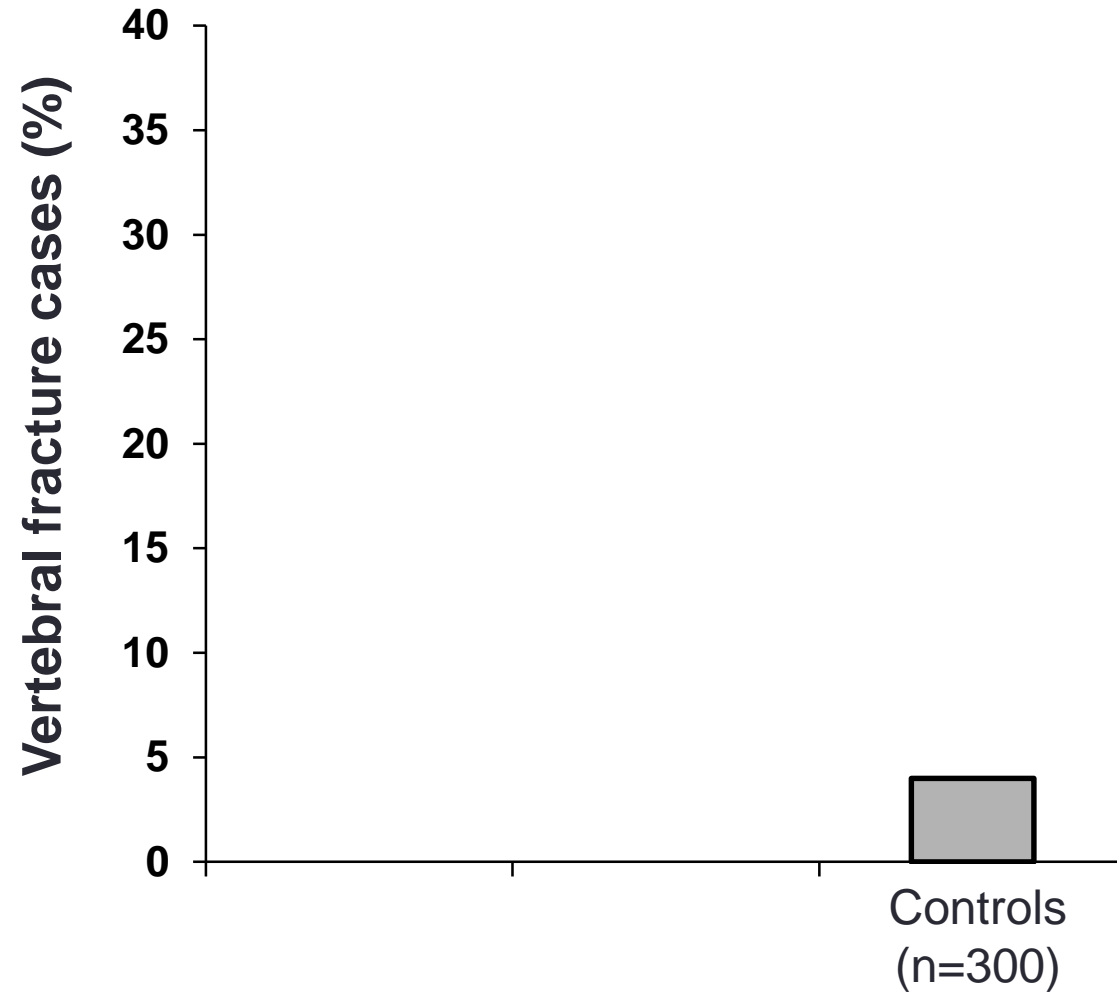
Fracture risk in PHPT -2-



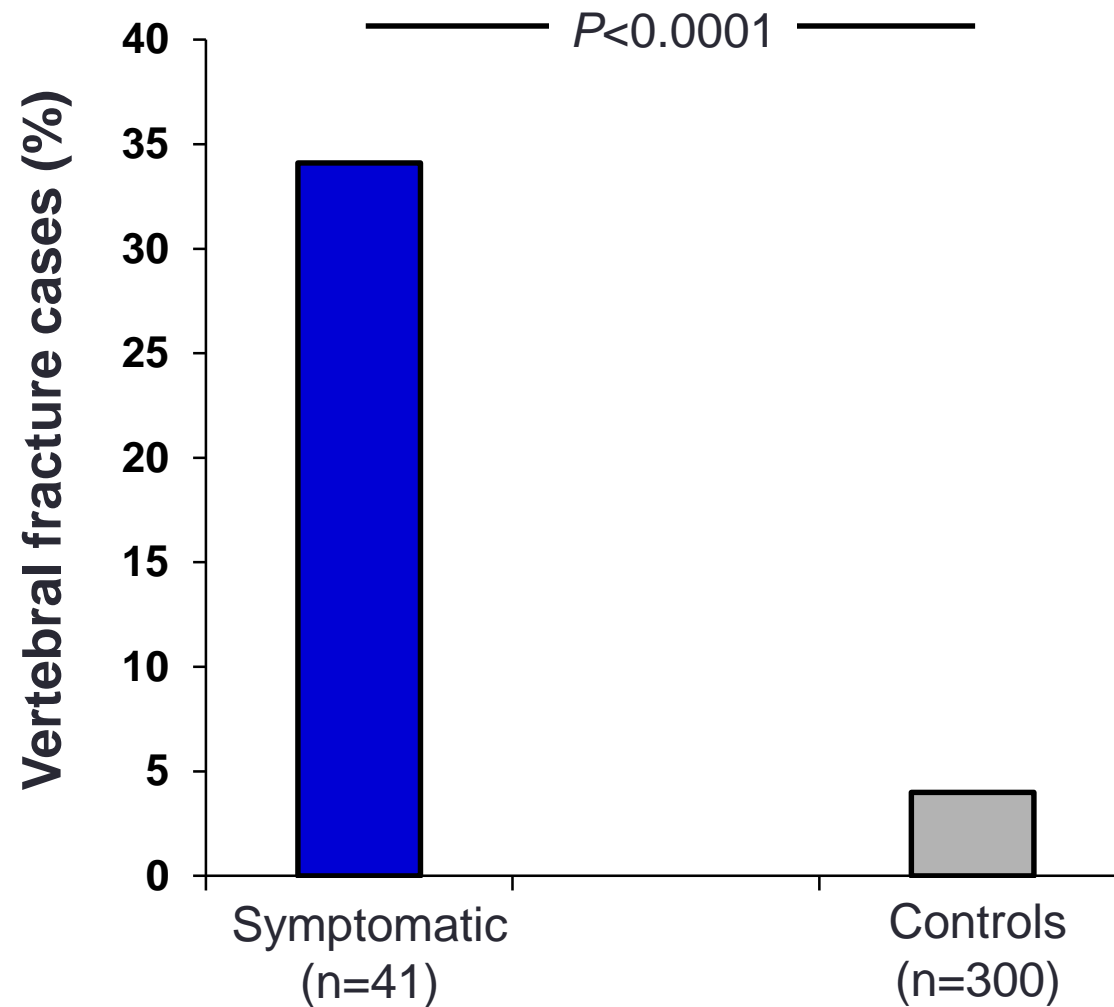
Fracture risk in PHPT -2-



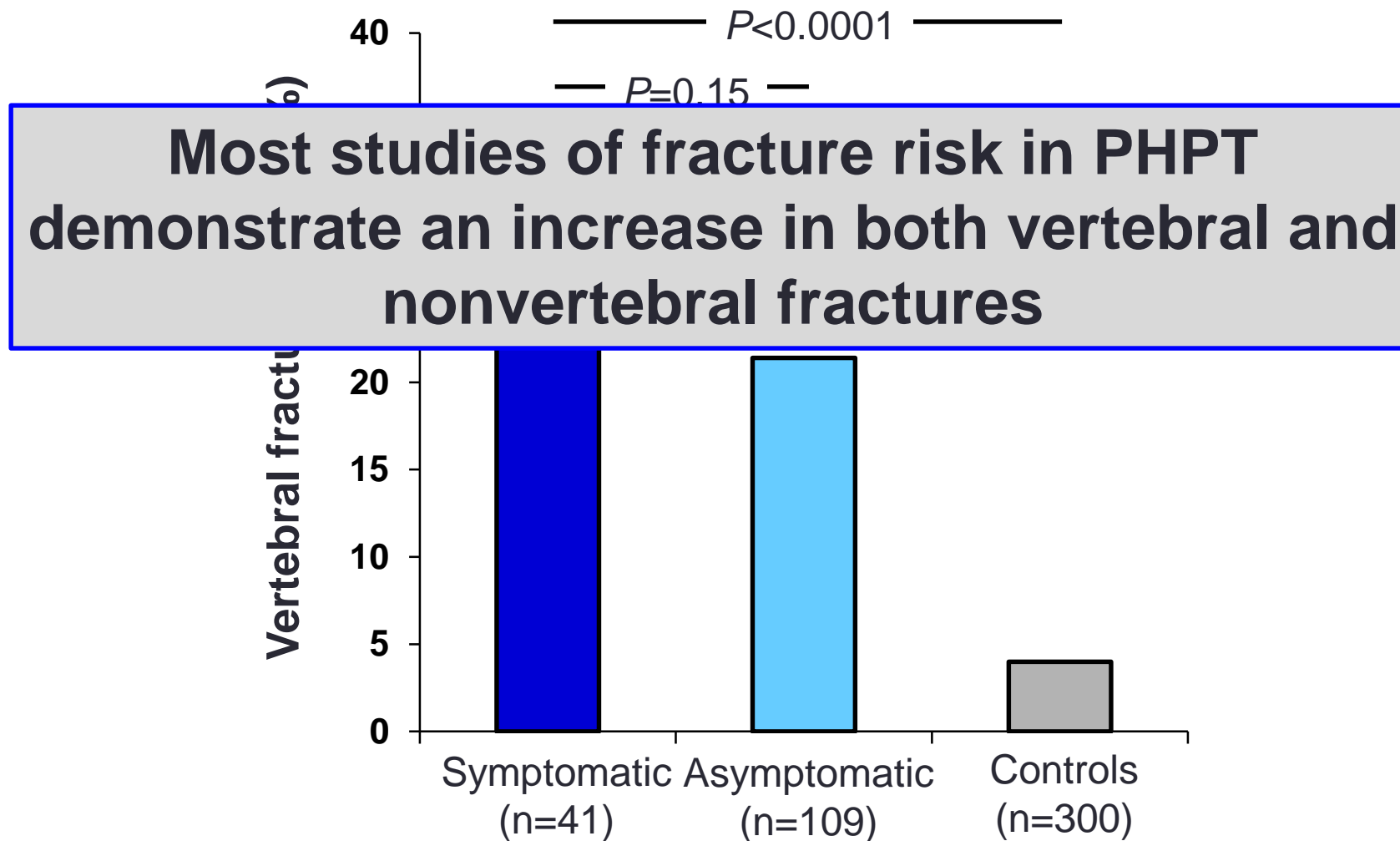
Fracture risk in PHPT -3-



Fracture risk in PHPT -3-

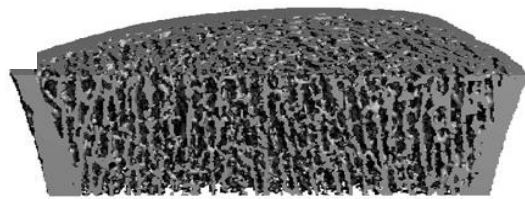


Fracture risk in PHPT -3-

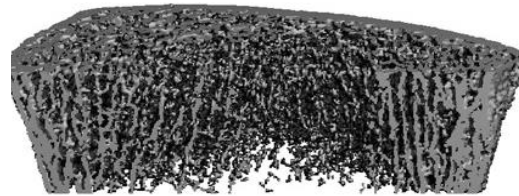


Trabecular bone is also affected in asymptomatic PHPT

- High-resolution peripheral quantitative computed tomography (HRpQCT) is a non-invasive methodology to determine bone quality
- Using HRpQCT, two groups have demonstrated abnormalities in both cortical and trabecular bone in women with PHPT



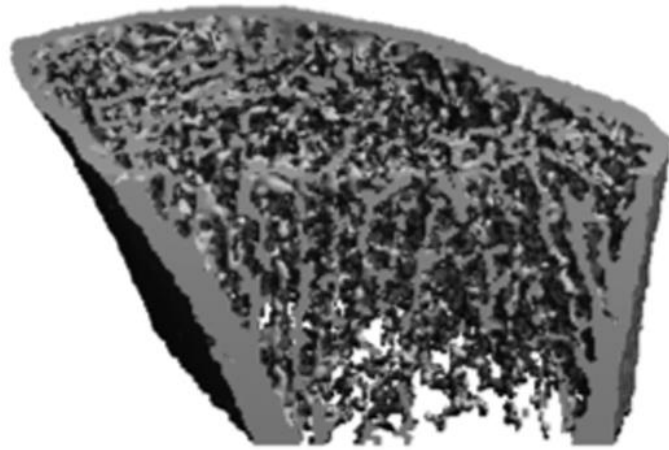
Normal



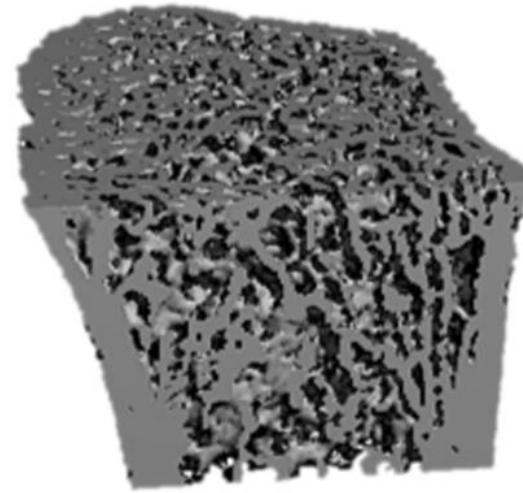
Osteoporotic



Microstructure is abnormal in asymptomatic PHPT



PHPT



Matched control

Microstructure is abnormal in asymptomatic PHPT

HRpQCT Parameters

Total Area

Total vBMD

Cortical *and* trabecular indices are reduced at the radius and tibia in asymptomatic PHPT

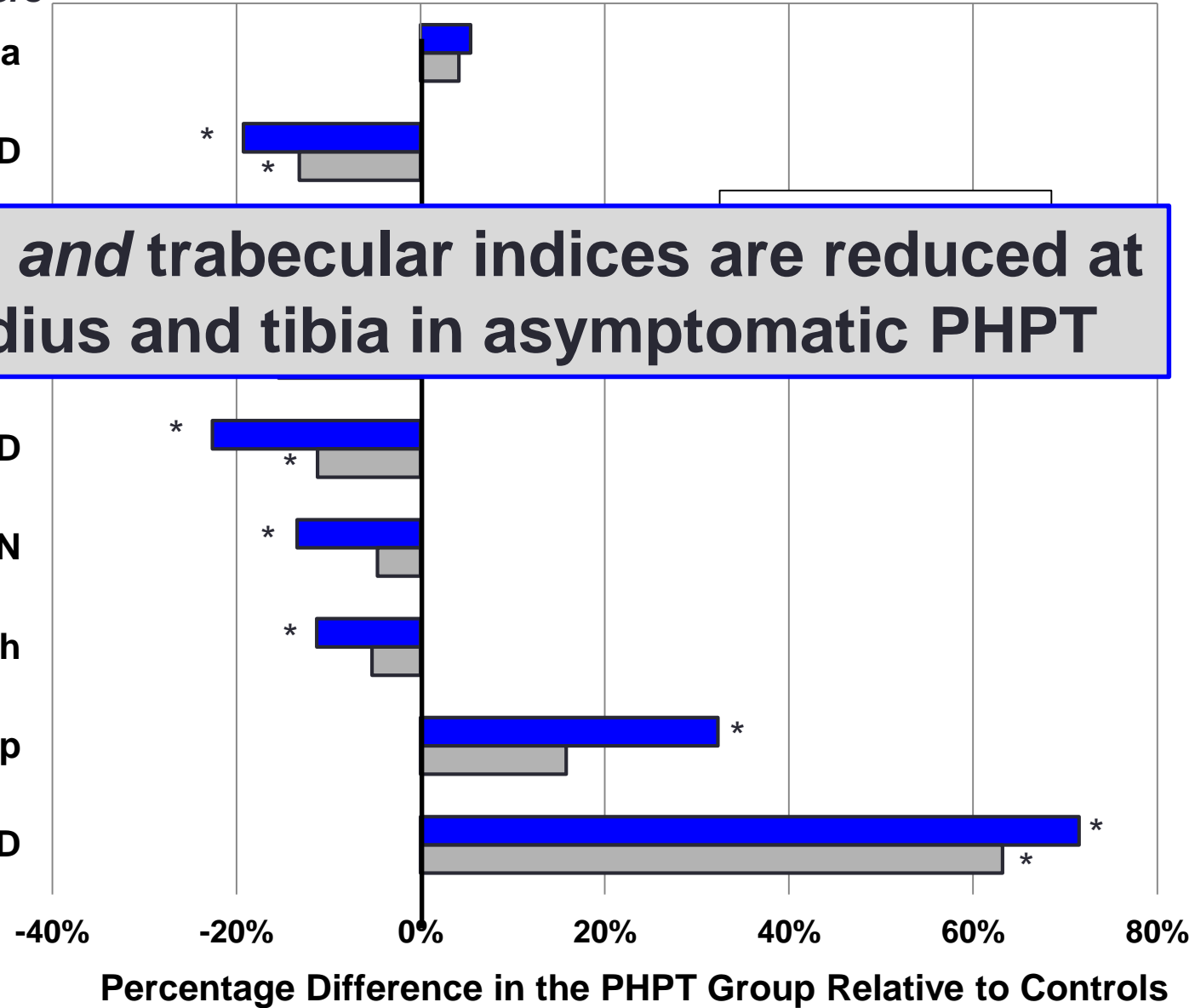
Tb.vBMD

Tb.N

Tb.Th

Tb.Sp

Tb.Sp.SD



Surgical guidelines for asymptomatic PHPT

Index	Third workshop (2008)	Fourth workshop (2013)
Age	<50 years	<50 years
Serum calcium	>1.0 mg/dL above normal	>1.0 mg/dL above normal
Skeletal	<ul style="list-style-type: none">• T-score <-2.5 at any site• Clinical fragility fracture	<ul style="list-style-type: none">• T-score <-2.5 at any site• Clinical fragility fracture➤ Vertebral fracture by vertebral fracture assessment (VFA), X-ray, CT or MRI

Recommendation 3-4: Parathyroidectomy is indicated in patients with PHPT and osteoporosis, fragility fracture, or evidence of vertebral compression fracture on spine imaging (strong recommendation; high-quality evidence)

Surgical guidelines for asymptomatic PHPT

Index	Third workshop (2008)	Fourth workshop (2013)
Age	<50 years	<50 years
Serum calcium	>1.0 mg/dL above normal	>1.0 mg/dL above normal
Skeletal	<ul style="list-style-type: none"> • T-score <-2.5 at any site • Clinical fragility fracture 	<ul style="list-style-type: none"> • T-score <-2.5 at any site • Clinical fragility fracture ➤ Vertebral fracture by VFA, X-ray, CT or MRI
Renal	Creatinine clearance <60 cc/min [24-hour urine not recommended]	<ul style="list-style-type: none"> • eGFR <60 cc/min ➤ Kidney stone by X-ray, CT, or US ➤ Urinary calcium >400 mg + other urinary indices of increased stone risk

Recommendation 3-3: Parathyroidectomy is indicated for objective evidence of renal involvement, including silent nephrolithiasis on renal imaging, nephrocalcinosis, hypercalciuria (24-hour urine calcium level >400 mg/dL) with increased stone risk, or impaired renal function (glomerular filtration rate <60 mL/min) (weak recommendation; low-quality evidence)

Recommendations: Calcium and vitamin D intake

Nutritional elements

- Calcium intake should follow national guidelines
- 25-hydroxyvitamin D levels >20 ng/mL (>50 nmol/L) using initial doses of 600-1000 IU daily
- Monitor serum and urine calcium with vitamin D repletion

Recommendation 5-1: Most patients with PHPT should follow Institute of Medicine guidelines for calcium intake (strong recommendation; moderate quality evidence)

Recommendation 5-2: Prior to parathyroidectomy, patients with PHPT who are vitamin D deficient can safely begin vitamin D supplementation (weak recommendation; low quality evidence)

Phenotypes of PHPT

Before 1970:

A disease of bones, stones, groans, and moans

After 1970:

A disease with primarily biochemical and densitometric signatures

After 2000:

A disease that may present at first with a more subtle biochemical signature – elevated PTH levels with normal serum calcium

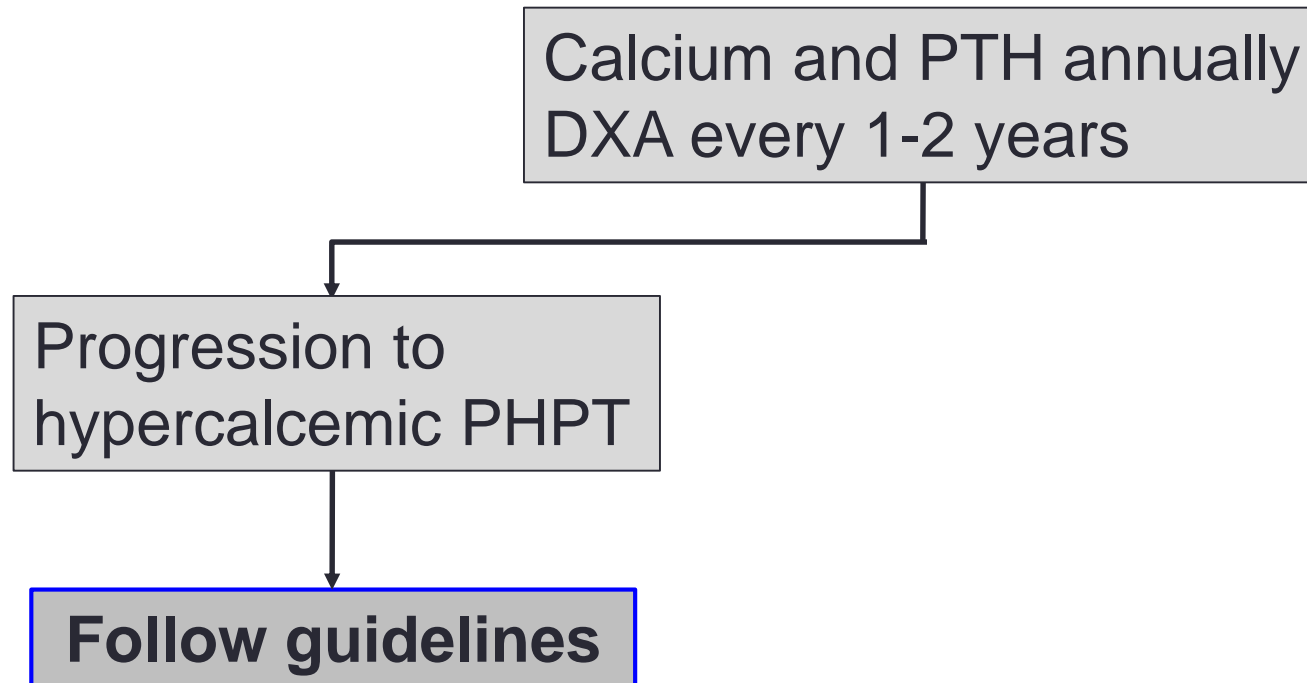
Diagnostic features of normocalcemic PHPT

- Elevated PTH
- Normal albumin-adjusted serum calcium
- Normal ionized calcium
- Corrected and ionized calcium ALWAYS
NORMAL

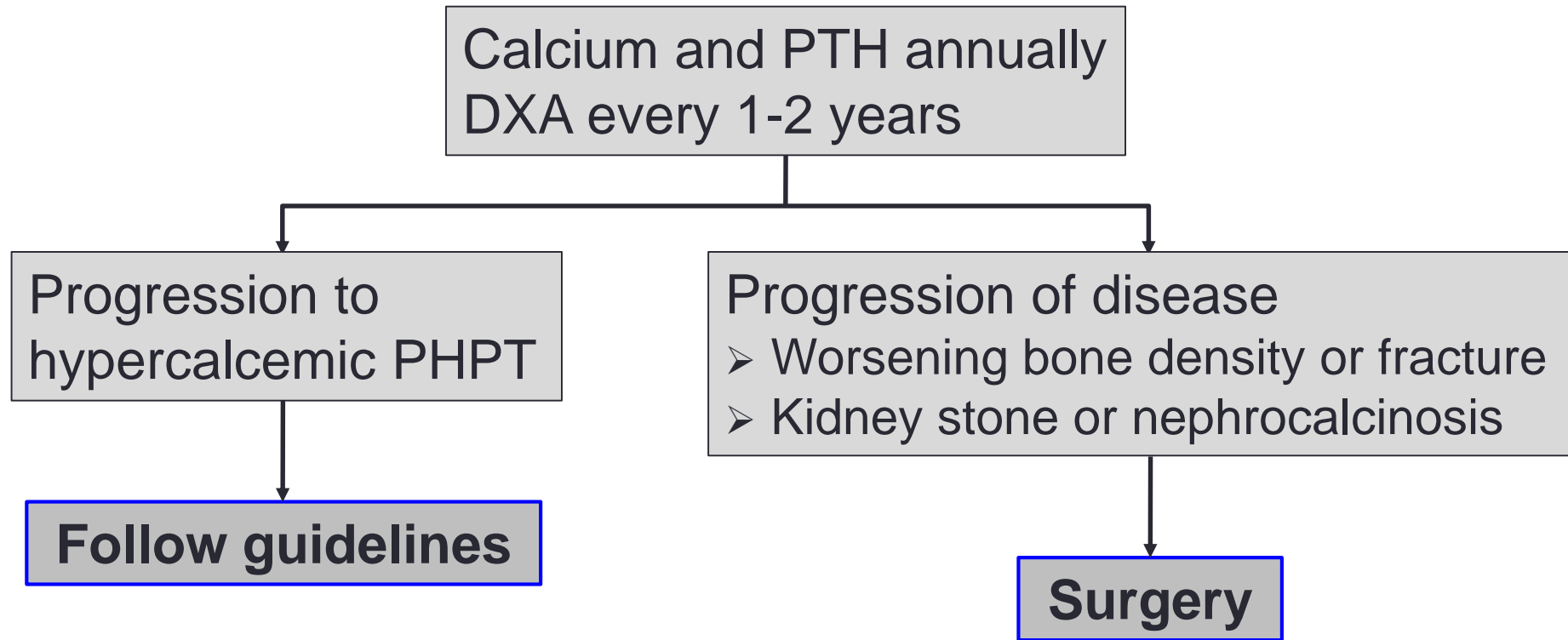
Exclude secondary hyperparathyroidism

- Vitamin D deficiency
 - Minimal goal level should be 20 ng/mL (50 nmol/L) but desirable >30 ng/mL (>75 nmol/L)
- Renal insufficiency
 - eGFR <60 cc/min
- Medications
 - Thiazide or loop diuretics, lithium, bisphosphonates, denosumab
- Hypercalciuria
- Malabsorption

Management of asymptomatic normocalcemic PHPT



Management of asymptomatic normocalcemic PHPT



Management of normocalcemic PHPT

- Bone density in patients with normocalcemic PHPT increases with alendronate treatment¹
- Imaging studies less likely to localize a parathyroid lesion^{2,3}
- Higher percentage of multiglandular disease in normocalcemic versus hypercalcemic PHPT
 - 13 vs 7%; $p < 0.05$ ²
 - 45 vs 9%; OR 8.17 (95% CI 4.49-14.83)³
- Patients with normocalcemic disease have similar improvements in bone density as hypercalcemic patients following parathyroid surgery^{4,5}

¹Cesareo R, et al. Osteoporos Int 2015;26:1295-1302; ²Šiprová H, et al. Endocr Pract. 2016;22:294-301; ³Lim JY, et al. Surgery 2017;161:70-77;

⁴Koumakis E, et al. J Clin Endocrinol Metab 2013;98:3213-3220; ⁵Traini E, et al. Langenbecks Arch Surg 2018;403:317-323

Medical management of PHPT

- Observation
- Pharmacological approaches

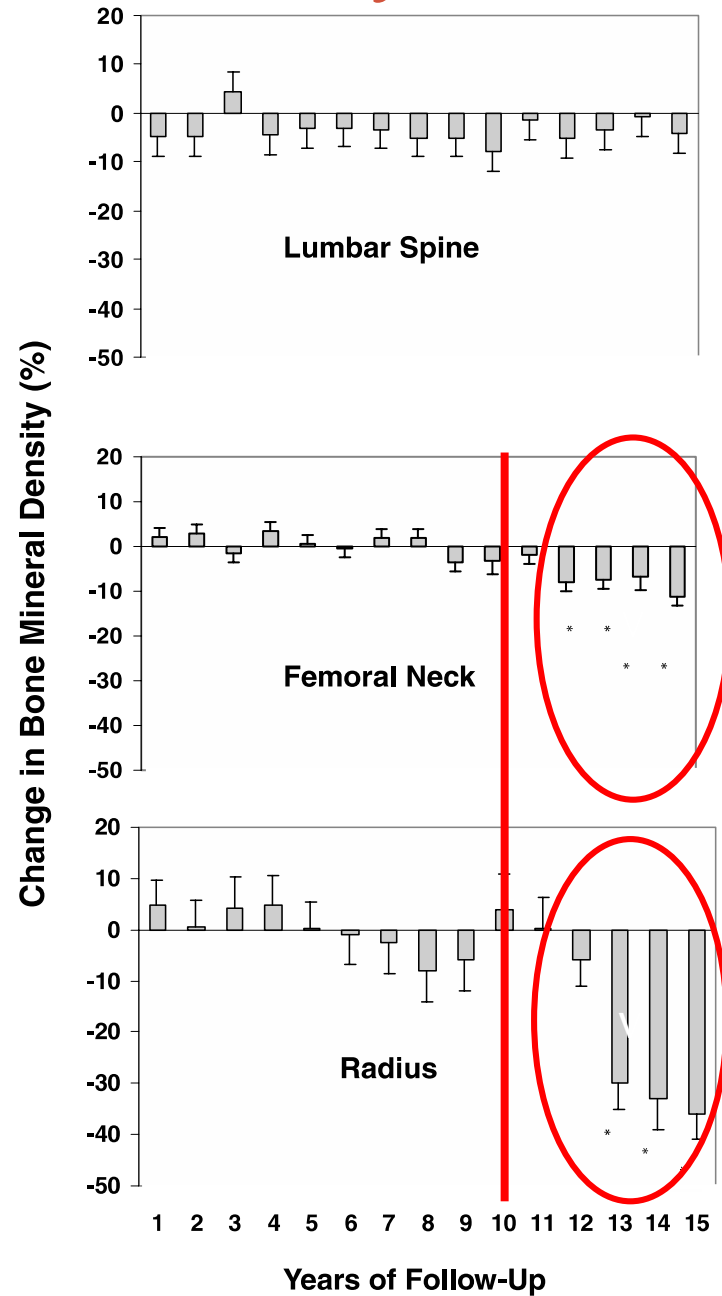
15-year natural history without surgery

Index	Baseline	5 years	10 years	13 years	15 years
Calcium	10.5 ± 0.1	10.7 ± 0.1	10.8 ± 0.2	11.0 ± 0.2	11.1 ± 0.2
PTH	122 ± 10	119 ± 12	123 ± 14	124 ± 16	121 ± 18
25-hydroxyvitamin D	21 ± 1	22 ± 2	22 ± 3	21 ± 3	20 ± 4
1,25-dihydroxyvitamin D	50 ± 2	58 ± 3	54 ± 6	40 ± 5	48 ± 7
Urine calcium	238 ± 19	215 ± 23	185 ± 32	247 ± 36	202 ± 36

15-year natural history without surgery

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15-year natural history without surgery -2-

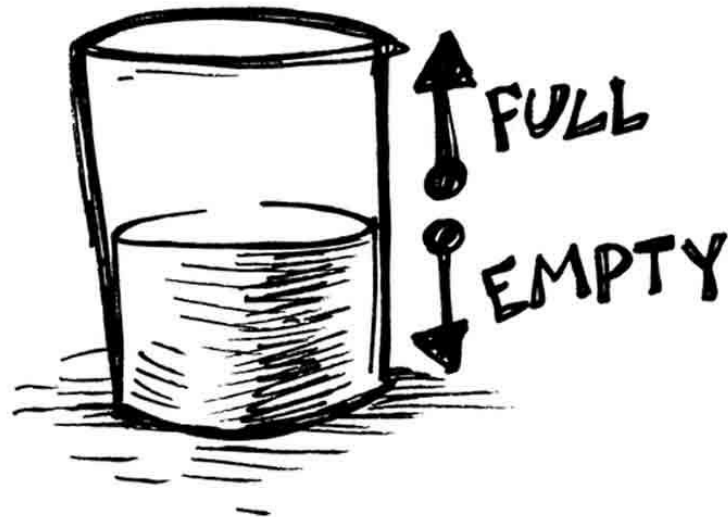


15-year natural history without surgery -3-

37% of patient developed one or more indications for surgery during 15 years of monitoring (nephrolithiasis, hypercalcemia, or reduced bone mineral density)

15-year natural history without surgery -3-

63% of patients did not develop an indication for surgery during 15 years of monitoring (nephrolithiasis, hypercalcemia, or reduced bone mineral density)



Pharmacologic approaches to PHPT

- When?
 - Surgery is indicated but medically contraindicated or patient declines
- Which agent?
 - The surgical indication can be ameliorated by the drug (e.g., severe hypercalcemia, reduced bone density)
 - Cinacalcet is the only approved agent for therapy of hypercalcemia in the US and EU
 - Other agents that have been studied include: estrogen, raloxifene, alendronate

Pharmacologic approaches to PHPT

Agent	Serum calcium	PTH	Bone density	
Estrogen ¹	↔	↔	↔	
Raloxifene ²	↓	↔	↔	
Alendronate ³	↔	↔	↑↑↑	Fracture data lacking
Cinacalcet* ⁴	↓↓↓	↓	↔	
Cinacalcet + Alendronate ⁵	↓↓↓	↓	↑↑↑	Fracture data lacking

*The only agent approved for PHPT in the US and EU

Recommendations: Pharmacologic management

- ❑ For the control of hypercalcemia, cinacalcet is the treatment of choice
- ❑ To improve BMD, bisphosphonate therapy is recommended
 - The best evidence is for the use of alendronate
- ❑ To reduce the serum calcium and improve BMD, combination therapy with both agents is reasonable, but strong evidence for efficacy is lacking

* Recommendation 3-12: Operative management is more effective and cost-effective than either long-term observation or pharmacologic therapy (strong recommendation; moderate quality evidence)

Surgical management of PHPT

- Surgical approaches include minimally invasive parathyroidectomy with intraoperative PTH and full exploration
 - In the modern era, MIP with iPTH has helped achieve cure rates of 97-99%

“The most important preoperative localization challenge in PHPT is to locate the parathyroid surgeon!” – John Doppman, 1975

Following successful parathyroid surgery...

- Serum calcium
- PTH
- 25-hydroxy- and 1,25-dihydroxyvitamin D
- Urine calcium
- Risk of nephrolithiasis
- Bone markers (resorption and formation)
- Bone density
- Bone microarchitecture

→ ***Normalize or return towards normal***

Are the scales tipping toward surgery?

Surgery

- 15-year natural history
- Vitamin D deficiency
- Neurocognitive data?
- Cardiovascular data?
- Cortical and trabecular abnormalities and improvement following surgery
- Better imaging techniques
- Improvements in surgical technique
- Patient preference

Medical management

- 15-year natural history
- Use of vitamin D
- Medical alternatives
- Patient preference



Would a noninvasive method of “parathyroidectomy” (ultrasound guided microwave ablation) further tip the scale?

Both options are important to consider in each patient

Key Points

- Guidelines for parathyroid surgery have been revised consistent with the latest new information
- Non-surgical management may be appropriate for individuals who do not meet surgical criteria or if there are contraindications to surgery
- Surgery may also be appropriate for individuals who do not meet surgical criteria, if there are no medical contraindications

Acknowledgements

- Dr. John Bilezikian

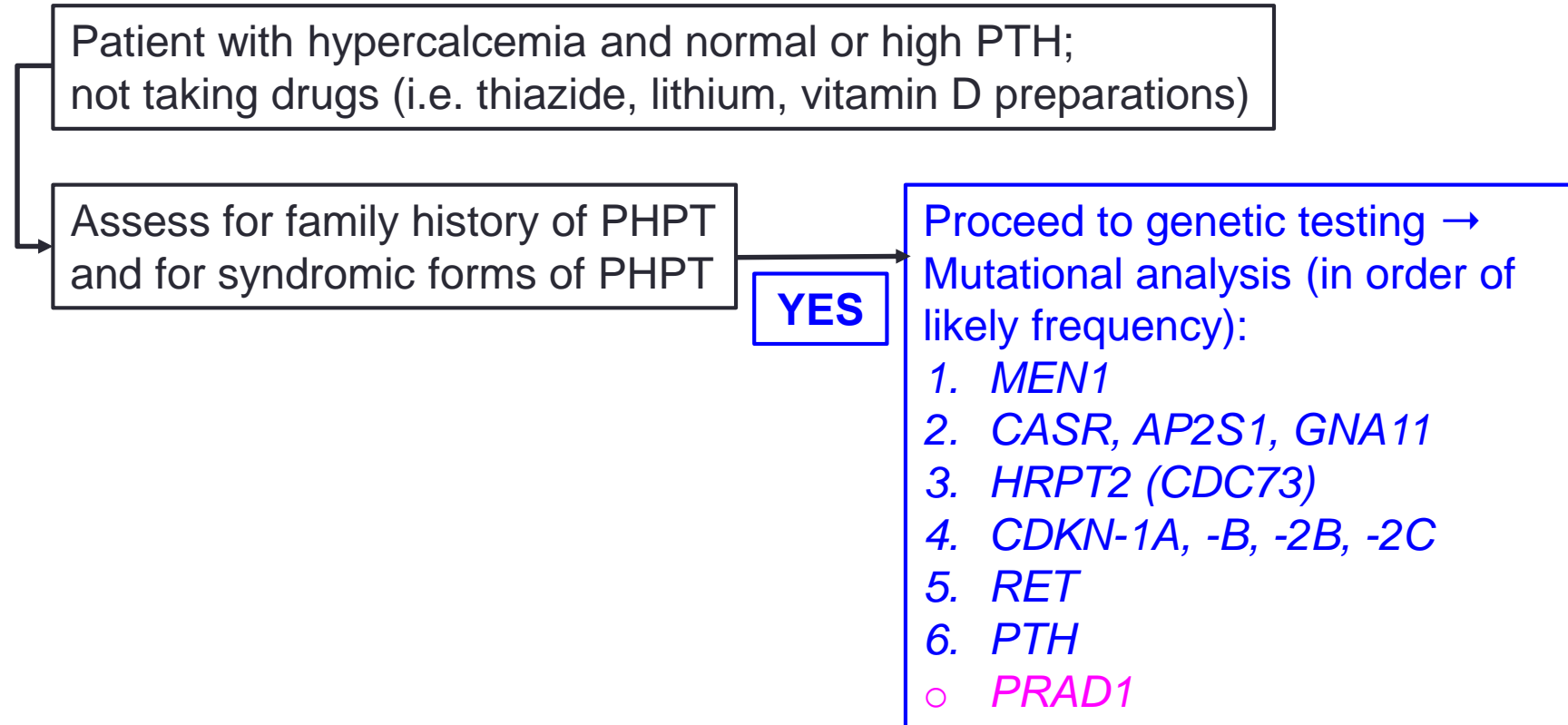
THANK YOU

Differential diagnosis

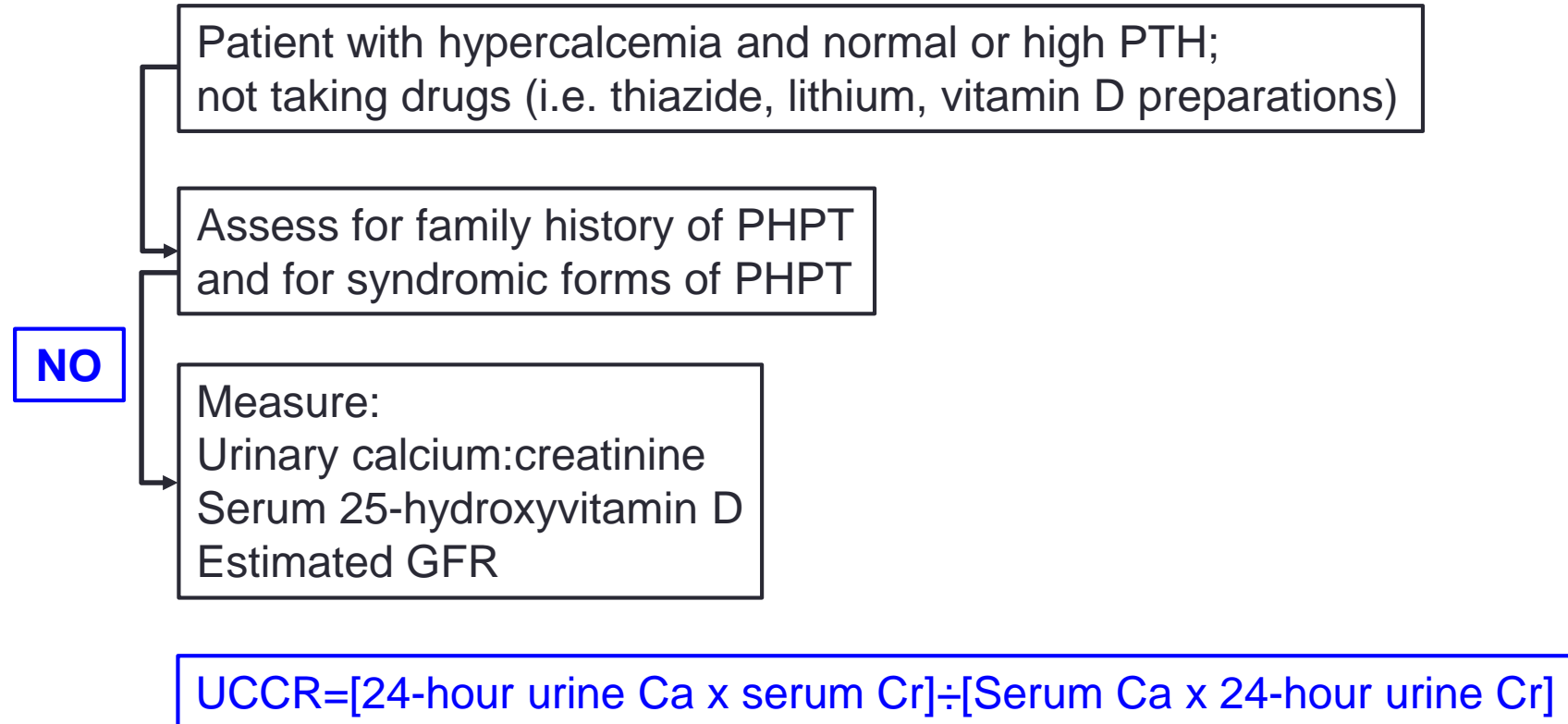
If low PTH, exclude biotin supplements

Patient with hypercalcemia and normal or high PTH;
not taking drugs (i.e. thiazide, lithium, vitamin D preparations)

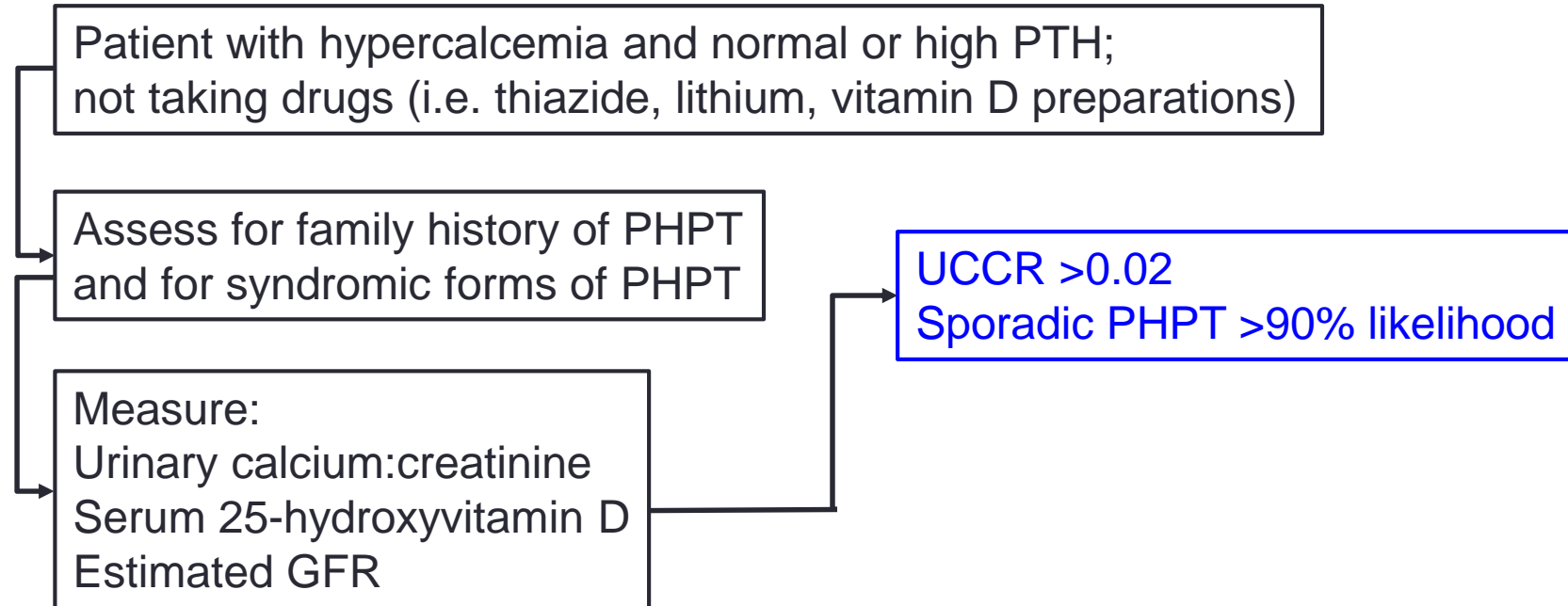
Differential diagnosis



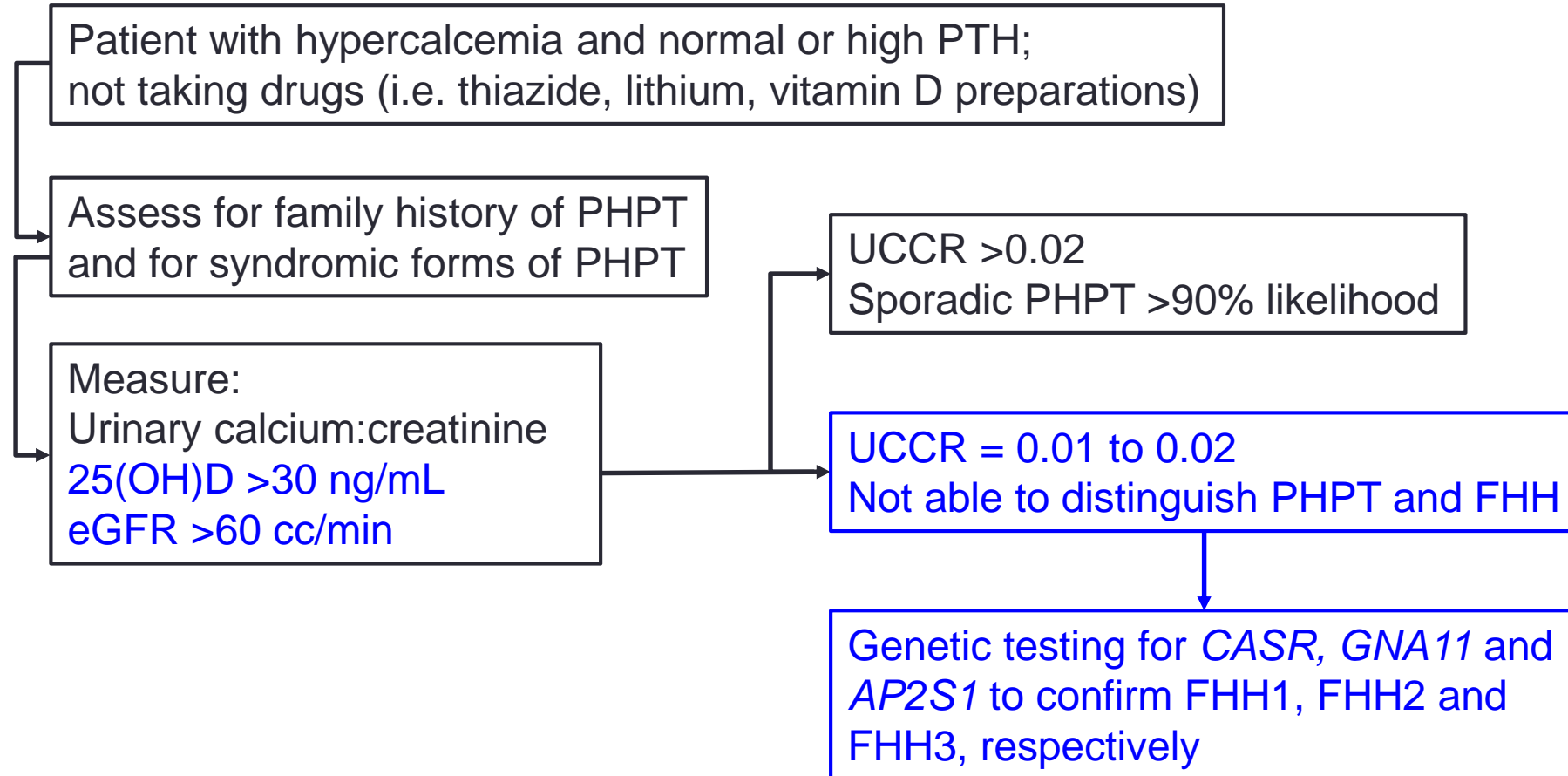
Differential diagnosis



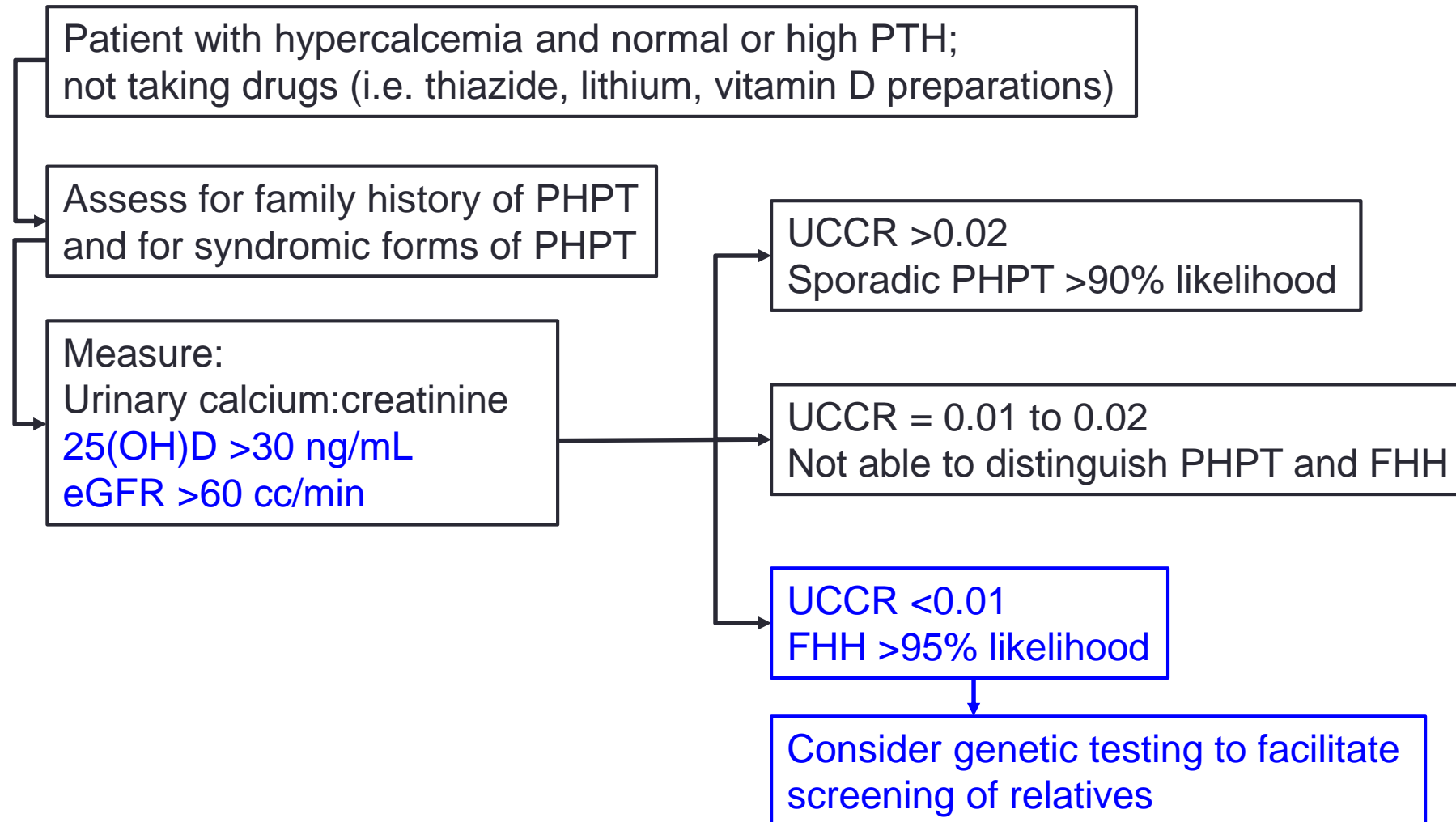
Differential diagnosis



Differential diagnosis



Differential diagnosis



Monitoring guidelines for asymptomatic PHPT

Index	Third workshop (2008)	Fourth workshop (2013)
Serum calcium	Annually	Annually
Skeletal	DXA: Every 1-2 years	<ul style="list-style-type: none">• DXA: Every 1-2 years• Imaging if clinically indicated
Renal	Annual monitoring of creatinine clearance	<ul style="list-style-type: none">• Annual monitoring of eGFR• Stone risk profile or abdominal imaging if clinically indicated

Indications for surgery during monitoring

Index	Fourth workshop (2013)
Serum calcium	>1 mg/dL above the normal limit
Skeletal	<ul style="list-style-type: none">• T-score <-2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius; or a significant reduction in BMD*• Vertebral fracture by X-ray, CT, MRI or VFA
Renal	<ul style="list-style-type: none">• eGFR <60 cc/min• Clinical development of a kidney stone or by imaging (X-ray, ultrasound, or CT)

*A significant change is defined by a reduction that is greater than the least significant change (LSC) as defined by the International Society for Clinical Densitometry. If the reduction is > LSC of the measurement to a T-score that is <-2.5 then, surgery is recommended. If the patient demonstrates a progressive reduction in BMD that exceeds the LSC at any site and is between -2.0 and -2.5, the physician may opt to recommend surgery even though guidelines have not been strictly met.