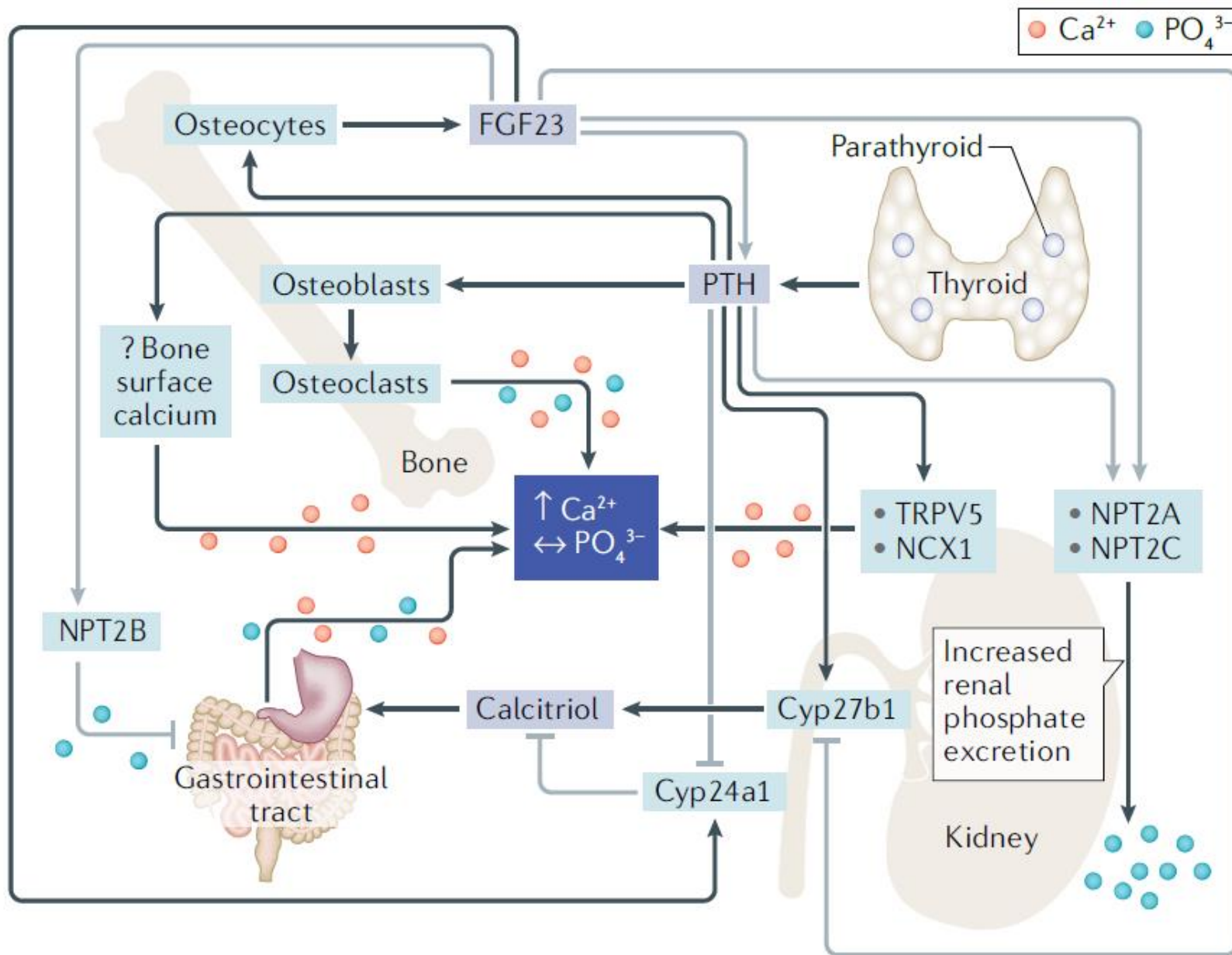


ΠΡΩΤΟΠΑΘΗΣ ΥΠΕΡΠΑΡΑΘΥΡΕΘΕΙΔΙΣΜΟΣ

Συμεών Τουρνής
Ενδοκρινολόγος

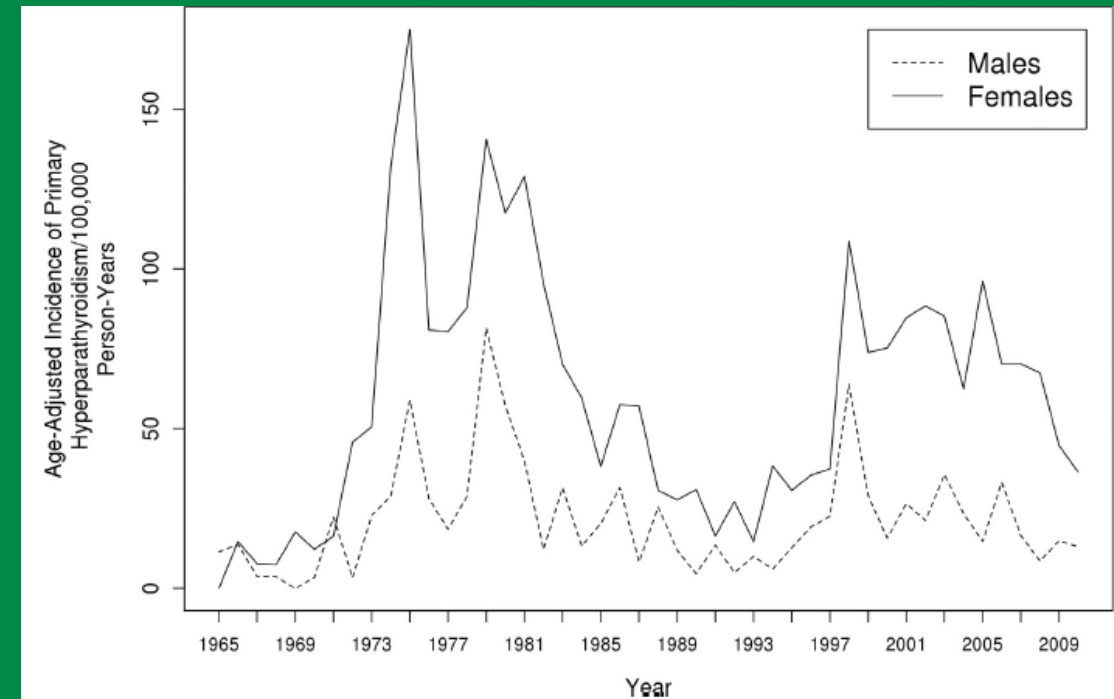
Ομοιόσταση Ασβεστίου-Φωσφόρου

Arnold A, et al.
NRE 2021



Επιδημιολογία σποραδικού ΠΥ

- Επιπολασμός: 0,86% (ΗΠΑ), Γυναίκες 55-75 ετών εως 2.6 %.
- Peak: 6^η -7^η δεκαετία
- 23/10000 F - 8,5/10000 M
- Φύλο: 3-4:1
- Risk factors
 - Ακτινοβολία
 - Λίθιο [Σε διπολική διαταραχή/ lit vs. no lit 26.2% (82/313) vs.1.4% (2/137)]
 - bipolar disorder not treated with lithium
 - Παχυσαρκία
 - Μειωμένη φυσική δραστηριότητα
 - Υποβιταμίνωση D?
 - Ασβεστιουρία?
 - Κληρονομικές μορφές: 5-10%



Bone 2015;73:1-7

Ταξινόμηση

Κλινική

- Κλασσικός συμπτωματικός ΡΗΡΤ
- Ασυμπτωματικός ΡΗΡΤ

Βιοχημική

- **Κλασσικός ΡΗΡΤ:** High Ca, High PTH
- **Normohormonal ΡΗΡΤ:** High Ca, Normal PTH (> 40 pg/ml)
 - 25% of all cases
 - Multigland disease
 - ΔΔ από FHH
- **Νορμοασβεστιαμικός ΡΗΡΤ:** Normal Ca, High PTH (> 65 pg/ml)

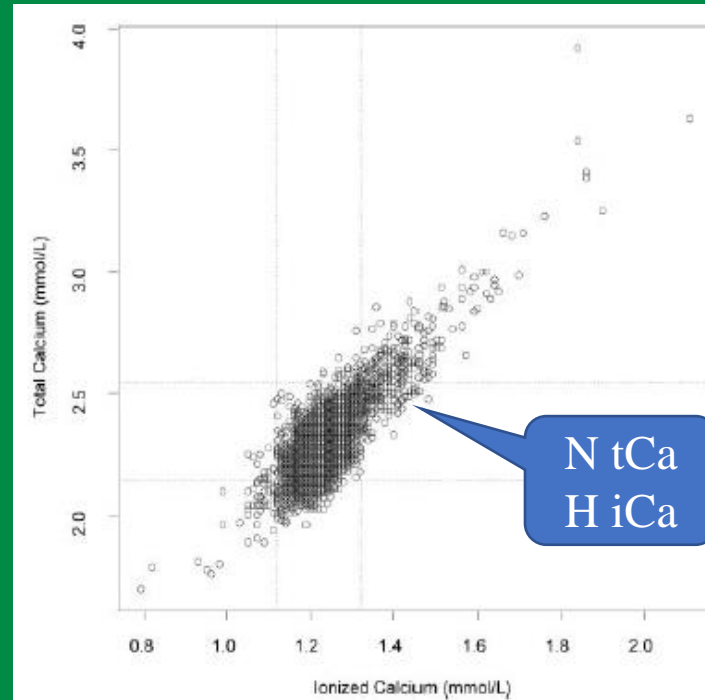
Normocalcemic Hyperparathyroidism: A Heterogeneous Disorder Often Misdiagnosed?

Guido Zavatta^{1,2}  and Bart L Clarke² 

JBMR plus 2020

- Φυσιολογικά επίπεδα ολικού και ιονισμένου ασβεστίου με σταθερά αυξημένη PTH για ικανό χρονικό διάστημα
- Επιπολασμός 0,4-11%
- Αποκλεισμός:
 - Υποβιταμίνωση D (> 30 ng/ml)
 - ΧΝΝ (> 60 ml/min)
 - Φάρμακα (λίθιο, θειαζίδες, BSP, Denosumab)
 - Ασβεστιουρία
 - Σύνδρομο δυσαπορρόφησης ή ανεπαρκής πρόσληψη ασβεστίου

Ιονισμένο Ca- Διορθωμένο Ca



Total Normocalcemic PHPT (n=455)

I only

46/455

10%

Surg Proven PHPT (n=143)

I only

34/143

24%

↓ PTH, ηλικία, μέγεθος αδενώματος,

Misclassification of Calcium Status Based on Albumin-Adjusted Calcium Studies in a Tertiary Hospital Setting

Joel D. Smith,¹ Scott Wilson,^{2,3} and Hans G. Schneider^{1,3*}

Albumin-adjusted total calcium was calculated from a modified Payne formula (7), with the slope determined by an inhouse regression for our bromocresol purple albumin method against total calcium.

$$\begin{aligned} \text{Adjusted calcium}_{\text{SI units}} \text{ (mmol/L)} \\ &= \text{total calcium (mmol/L)} + 0.018 \\ &\times [40 - \text{albumin (g/L)}] \end{aligned} \quad (1)$$

$$\begin{aligned} \text{Adjusted calcium}_{\text{conventional units}} \text{ (mg/dL)} \\ &= \text{total calcium (mg/dL)} + 0.72 \\ &\times [4 - \text{albumin (g/dL)}] \end{aligned} \quad (2)$$

Adjustment for albumin can lead to overcorrection and falsely diagnosed hypercalcemia, in those with poor renal function and where albumin levels are less than 30 g/L.

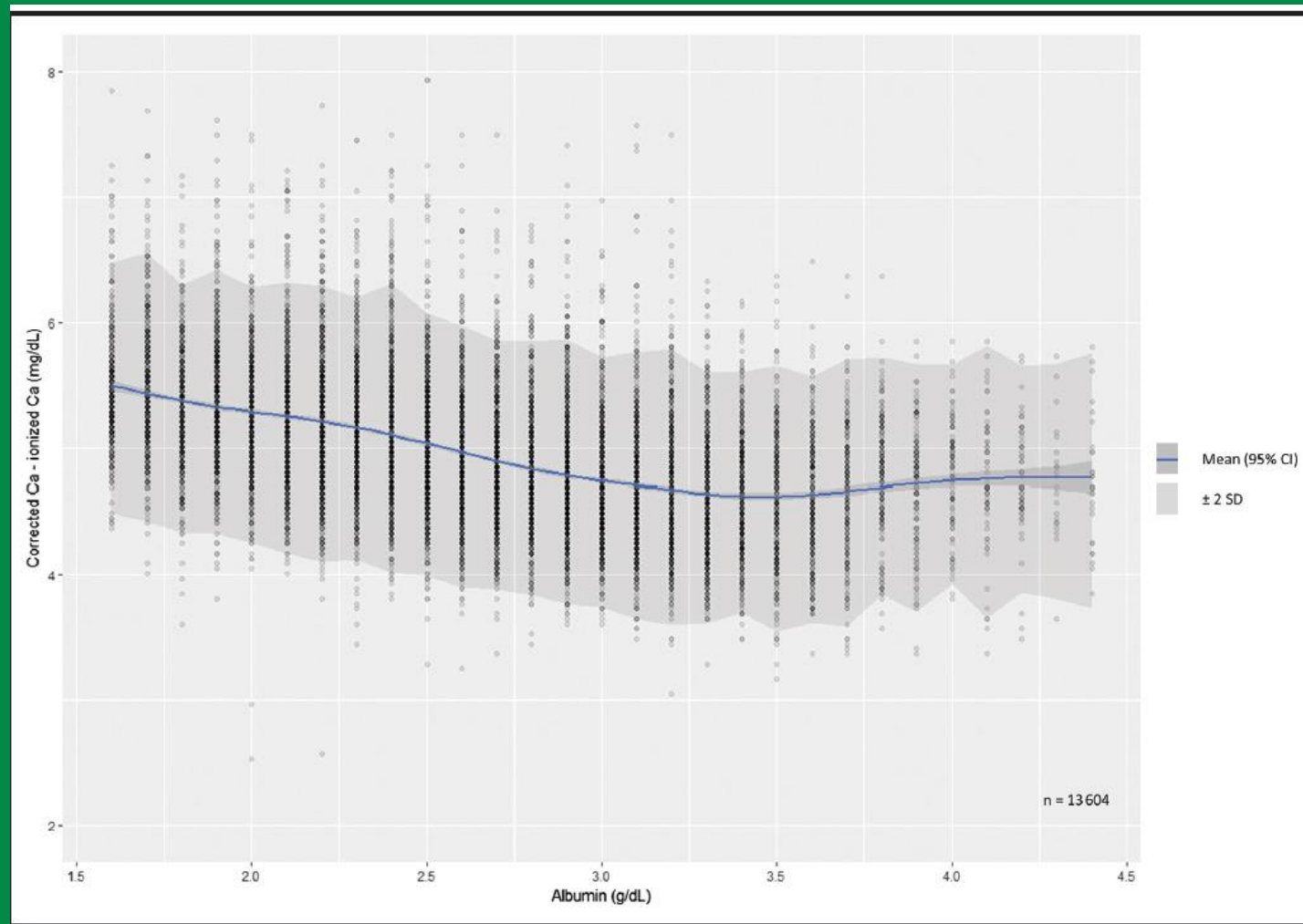
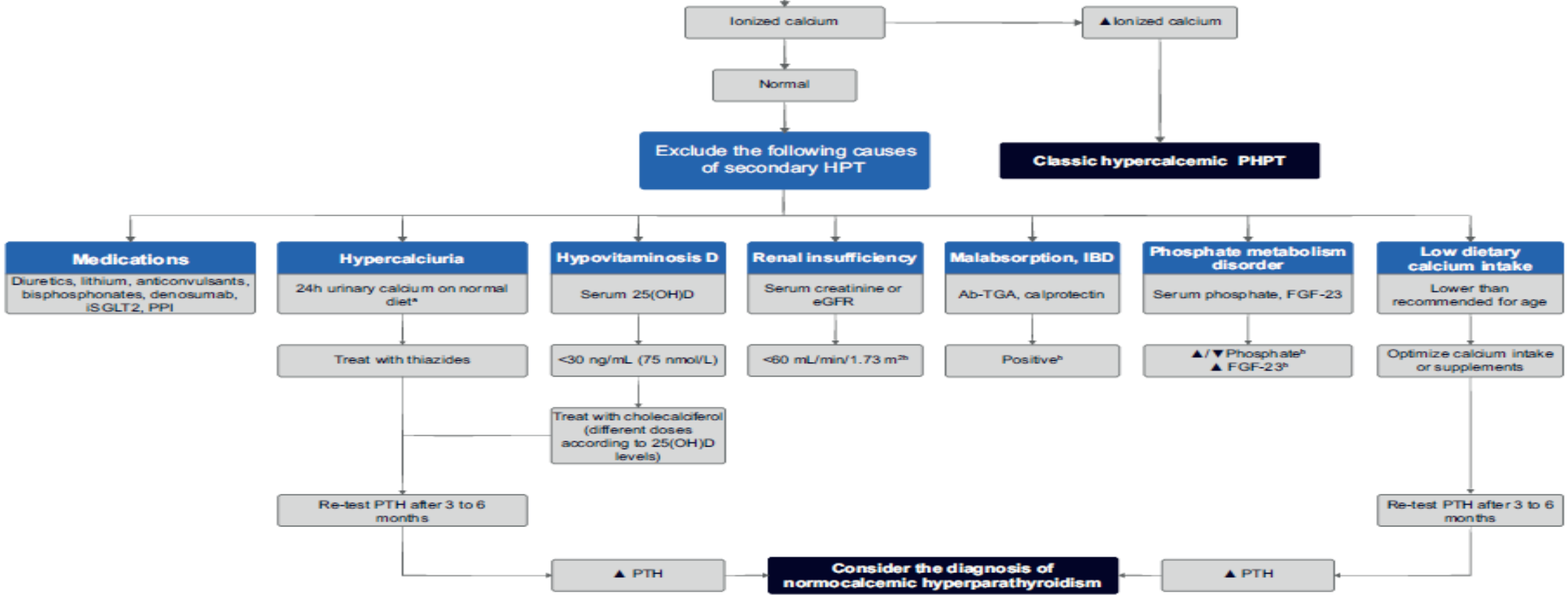


Fig. 1. Albumin-adjusted calcium minus ionized calcium for different albumin levels (24 months of retrospective data).

Approach to the patient with confirmed elevated PTH and normal corrected total calcium levels



In summary, normocalcemic PHPT must be diagnosed by exclusion, and laboratory testing over time is necessary to distinguish normocalcemic PHPT from secondary hyperparathyroidism. Evidence on the effect of parathyroidectomy (PTX) or any other management of normocalcemic PHPT is scarce, and there are no clear data on the natural history of normocalcemic PHPT. However, unless longitudinal studies prove the opposite, established normocalcemic variant of PHPT requires standard PHPT diagnostic procedures and surgical intervention should be considered only after experienced endocrine review; in this case, only if there are compelling indications and a surgical target.

TABLE 2 Syndromic and nonsyndromic monogenic disorders associated with hereditary hypercalcaemia/PHPT

	Estimated prevalence	Gene	Chrom. Pos	Inherit.	Variant type	Genetic testing strategy
Syndromic forms of PHPT						
Multiple endocrine neoplasia Type 1 (MEN1)	~1/30,000	<i>MEN1</i>	11q13.1	AD	ms, LOF, del ^a	Single gene/gene panel (MLPA)
Multiple endocrine neoplasia Type 2A (MEN2A)	~1/35,000	<i>RET</i>	10q11.21	AD	ms	Single gene/gene panel
Multiple endocrine neoplasia Type 4 (MEN4)	Rare (<1/million)	<i>CDKN1B</i> ^b	12p13.1	AD	ms, LOF	Single gene/gene panel
Hyperparathyroidism jaw tumor (HPT-JT) syndrome	Rare (<1/million)	<i>CDC73</i>	1q31.2	AD	ms, LOF, del ^a	Single gene/gene panel (MLPA)
Nonsyndromic forms of PHPT including FHH						
Familial isolated hyperparathyroidism (FIHP)	Uncertain	<i>GCM2</i> ^c	6p24.2	AD	ms,	Single gene/gene panel
	-	(<i>MEN1</i> ^c)	11q13.1	AD	ms, LOF	Single gene/gene panel (MLPA)
	-	(<i>CDC73</i> ^c)	1q31.2	AD	ms, LOF	Single gene/gene panel (MLPA)
	-	(<i>CASR</i> ^c)	3q13.33-q21.1	AD	ms, LOF	Single gene/gene panel
Familial hypocalciuric hypercalcemia Type 1 (FHH1)	~1/1-5,000	<i>CASR</i>	3q13.33-q21.1	AD	ms, LOF	Single gene/gene panel
Familial hypocalciuric hypercalcemia Type 2 (FHH2)	Rare	<i>GNA11</i>	19p13.3	AD	ms, (if-del)	Single gene/gene panel
Familial Hypocalciuric Hypercalcemia Type 3 (FHH3)	~1/13,000	<i>AP2S1</i>	19q13.32	AD	ms (Arg15)	Single gene/gene panel
Neonatal Severe Hyperparathyroidism (NSHPT)	Rare	<i>CASR</i>	3q13.33-q21.1	AR/AD	ms, LOF	Single gene/gene panel
Miscellaneous conditions associated with hypercalcaemia						
Infantile hypercalcaemia Type 1	Rare	<i>CYP24A1</i>	20q13.2	AR	LOF	Single gene/gene panel
Infantile hypercalcaemia Type 2	Rare	<i>SLC34A1</i>	5q35.3	AR	LOF	Single gene/gene panel
Hypophosphatasia	~1/100,000	<i>TNSALP</i>	1p36.12	AR (AD)	ms, LOF	Single gene/gene panel
Williams–Bueren Syndrome	~1/10,000	7q11.23 microdeletion	7q11.23	de novo, AD	1.5–1.8 Mb deletion	aCGH
Jansen metaphyseal chondrodysplasia (MC)	Rare	<i>PTH1R</i>	3p21.31	AD	ms	Single gene/gene panel

Familial PHPT

PHPT

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

FHH

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

Hyperparathyroidism-Jaw Tumour Syndrome

- Αδένωμα (τα) παραθυρεοειδών (65-90%)- 15-20% PC
- Οστεοποιοί ίνωμα γνάθου
- Όγκοι (νεφρός, μήτρα, θυρεοειδής, παγκρέατος, υπόφυσης)
- Αδρανοποιητικές μεταλλάξεις στο γονίδιο Cell Division Cycle 73 (CDC73)-
(Parafibromin/tumour suppressor protein)

GCM2 Variants in Familial and Multiglandular Primary Hyperparathyroidism

Sarah Vincze,¹ Nicholas V. Peters,² Chia-Ling Kuo,^{3, ID} Taylor C. Brown,^{2,4, ID} Reju Korah,² Timothy D. Murtha,² Justin Bellizzi,¹ Aaliyah Riccardi,^{1,5} Kourosh Parham,⁶ Tobias Carling,^{3,7} Jessica Costa-Guda,^{1,8, ID} and Andrew Arnold^{1,9}

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⁸Center for Regenerative Medicine and Skeletal Development, University of Connecticut School of Dental Medicine, Farmington, CT, USA

⁹Division of Endocrinology and Metabolism, University of Connecticut School of Medicine, Farmington, CT, USA

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Abstract

Context: Multiglandular and familial parathyroid disease constitute important fractions of primary hyperparathyroidism (PHPT). Germline missense variants of *GCM2*, a regulator of parathyroid development, were observed in familial isolated hyperparathyroidism and sporadic PHPT. However, as these previously reported *GCM2* variants occur at relatively high frequencies in the population, understanding their potential clinical utility will require both additional penetrance data and functional evidence relevant to tumorigenicity.

Objective: Determine the frequency of *GCM2* variants of interest among patients with sporadic multigland or familial parathyroid disease and assess their penetrance.

Design and Patients: DNA-encoding PHPT-associated *GCM2* germline variants were polymerase chain reaction–amplified and sequenced from 107 patients with either sporadic multigland or suspected/confirmed familial parathyroid tumors.

Results: *GCM2* variants were observed in 9 of 107 cases (8.4%): Y282D in 4 patients (6.3%) with sporadic multigland disease; Y394S in 2 patients (11.1%) with familial PHPT and 3 (4.8%) with sporadic multigland disease. Compared with the general population, Y282D was enriched 5.9-fold in multigland disease, but its penetrance was very low (0.02%). Y394S was enriched 79-fold in sporadic multigland disease and 93-fold in familial PHPT, but its penetrance was low (1.33% and 1.04%, respectively).

Conclusions: Observed in vitro–activating *GCM2* variant alleles are significantly overrepresented in PHPT patients with multiglandular or familial disease compared to the general population, yet penetrance values are very low; that is, most individuals with these variants in the population have a very low risk of developing PHPT. The potential clinical utility of detecting these *GCM2* variants requires further investigation, including assessing their possible role as pathogenic/low-penetrance alleles.

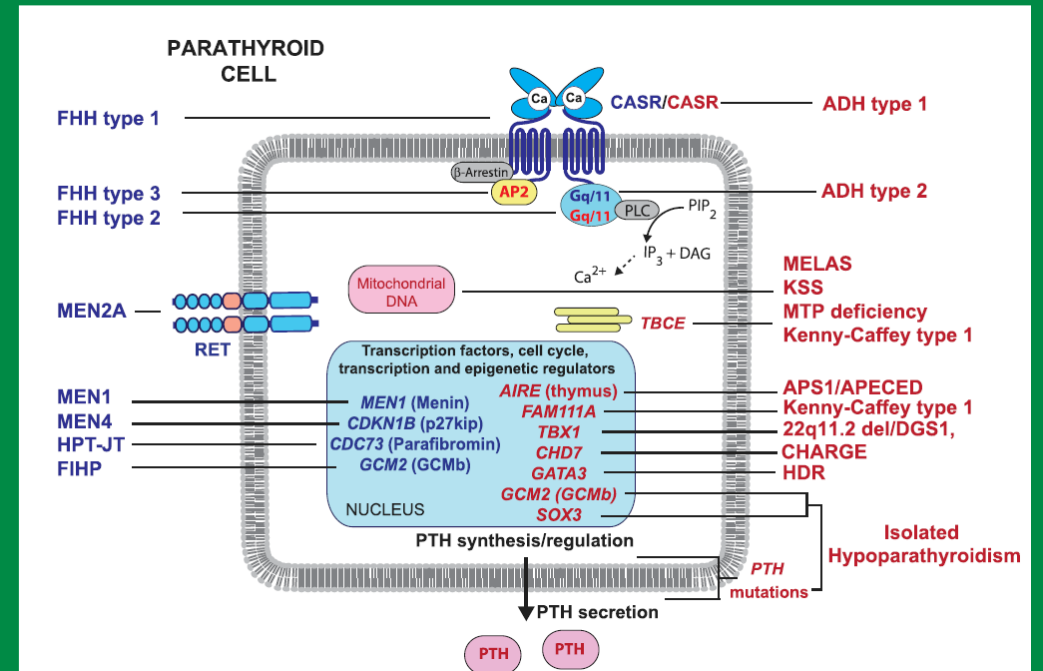
Key Words: familial isolated hyperparathyroidism, *GCM2*, parathyroid adenoma, primary hyperparathyroidism

Οικογενής Υποασβεστιουρική Υπερασβεστιαμία (FHH)

- Επιδημιολογία: 1/1000-5000
- Περιγράφεται και ως άτυπη μορφή ΡΗΡΤ (Marx SJ. JBMR 2018). Υπό αυτήν την έννοια αποτελεί το 2% των περιστατικών ΡΗΡΤ
- Σε ασθενείς μετά αποτυχία ΡΤχ:9-23% FHH
- FHH1:60-65%, FHH2:5%,FHH3:20% (Marx SJ, Horm Metab Resear 2017)
- Σποραδικές μεταλλάξεις: 15-30%

FHH-αιτιολογία

- FHH1
 - CaSR
 - Χρωμόσωμα 3q21
 - No genotype-phenotype correlation
- FHH2
 - GNA11 gene (G-protein subunit $\alpha 11$)
 - Χρωμόσωμα 19p13.3
- FHH3
 - AP2S1 gene (adaptor-related protein complex 2, sigma 1 (AP2 σ) subunit)
 - Χρωμόσωμα 19p13.3
- Επίκτητα παρούσα ab του συνδέονται με τον CaSR



FHH

Βιοχημική εικόνα

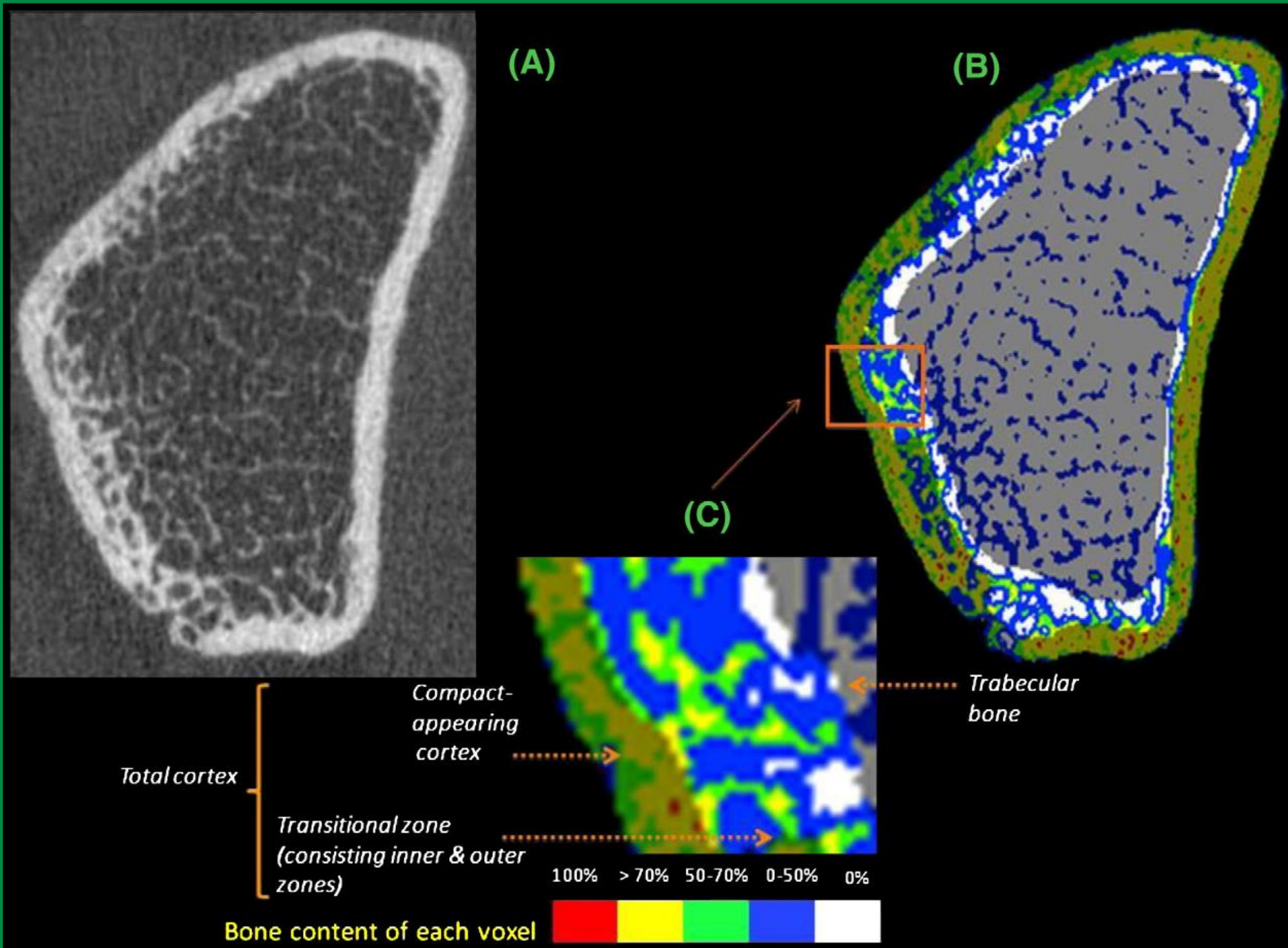
- Ca: ήπια αύξηση (<12 mg/dl)
- P: normal / low-normal
- Mg: high-normal
- PTH: normal- high-normal (80%)- 20% elevated
- 25(OH)D: normal
- 1,25(OH)D₂: normal/elevated
- CaCrClearR [(CaU*sCr)/(sCa*CrU)]: <0,01- 20-35% των ασθενών έχουν τιμή > 0,01
- Ορισμένοι προτείνουν γενετικό έλεγχο σε όλους τους ασθενείς με τιμή <0,02

Κλινική εικόνα

- Κατά κανόνα ασυμπτωματικοί
- Σοβαρότερη υπερασβεστιαμία: FHH3 (75% cognitive deficits in childhood)
- Μη ειδικά συμπτώματα: μυική αδυναμία, κόπωση, αρθραλγίες, δίψα, χονδρασβέστωση, παγκρεατίτις
- Αληθής PHPT
- Νοσηρότητα από εσφαλμένη παραθυρεοειδεκτομή
- Η βιοχημική εικόνα γενικά παραμένει σταθερή
- Cinacalcet επί συμπτωματικής υπερασβεστιαμίας
 - Marx SJ. (JCEM 2017): επί ca > 1 mg/dl άνω του ανώτερου φυσιολογικού.
- Κύηση:
 - Mother normal- infant affected (paternally): severe hypercalcemia
 - Mother affected-infant normal: transient neonatal hypoparathyroidism

Υπερπαραθυρεοειδική Οστική νόσος

- Συνολικά > 50%
- Κατεξοχήν προσβολή του φλοιώδους έναντι σπογγώδους οστού
- Αντιβράχιο > ισχίο > ΣΣ
- 15% των μετεμμηνοπαυσιακών γυναικών εμφανίζουν σημαντική απώλεια και στη ΣΣ
- 1/3 των ασθενών εμφανίζουν σπονδυλικές παραμορφώσεις κατά την αρχική εκτίμηση.
- Αύξηση του ρυθμού οστικής ανακατασκευής
- pQCT, HRpQCT, QCT: Διαταραχή αρχιτεκτονικής στο σπογγώδες και φλοιώδες
- TBS: μειωμένο σε PHPT, περαιτέρω μείωση επί σπονδυλικών καταγμάτων



Bone Material Strength Index as Measured by Impact Microindentation is Low in Patients with Primary Hyperparathyroidism

Manuela Schoeb,¹ Elizabeth M. Winter,¹ Maria A. Sleddering,¹ Mirjam A. Lips,¹ Abbey Schepers,² Marieke Snel,¹ and Natasha M. Appelman-Dijkstra¹

¹Center for Bone Quality, Department of Internal Medicine and division of Endocrinology, Leiden University Medical Center, Leiden, The Netherlands; and ²Center for Bone Quality and Center for Endocrine Tumors, Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands

e2532

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Table 2. Characteristics of patients with primary hyperparathyroidism with and without fragility fractures

	Fracture (n = 11)	No fracture (n = 26)	P value
Age, years	65.3 ± 11.3 (range 47-79)	60.4 ± 14.0 (range 37-84)	.319
Male/female	3/8	6/20	.786
BMI, kg/m ²	25.6 ± 2.1	26.0 ± 0.9	.832
Time since diagnosis, months	10 (IQR 2-69)	7 (IQR 2-51)	.682
Urolithiasis, n (%)	1 (9.0)	5 (19.2)	
Current medication use			
Antiresorptives, n (%)	3 (27.3)	6 (23.1)	.786
Calcimimetics, n (%)	0 (0.0)	7 (26.9)	.080
Calcium ^a , mmol/L	2.7 ± 0.1	2.7 ± 0.2	.600
PTH ^b , pmol/L	11.0 ± 0.8	10.0 ± 2.3	.544
Diagnosis by DXA			.057
Normal BMD, n (%)	1 (9.1)	5 (19.2)	
Osteopenia, n (%)	4 (36.4)	17 (65.4)	
Osteoporosis, n (%)	6 (54.5)	4 (15.4)	
LS BMD, g/cm ²	0.86 ± 0.16	0.94 ± 0.14	.115
T-Score LS	-1.6 ± 1.3	-0.9 ± 1.3	.170
FN BMD, g/cm ²	0.62 ± 0.08	0.73 ± 0.11	.007
T-Score FN	-2.2 ± 0.7	-1.2 ± 1.0	.009
BMSi	74.7 ± 6.0	79.6 ± 5.0	.015

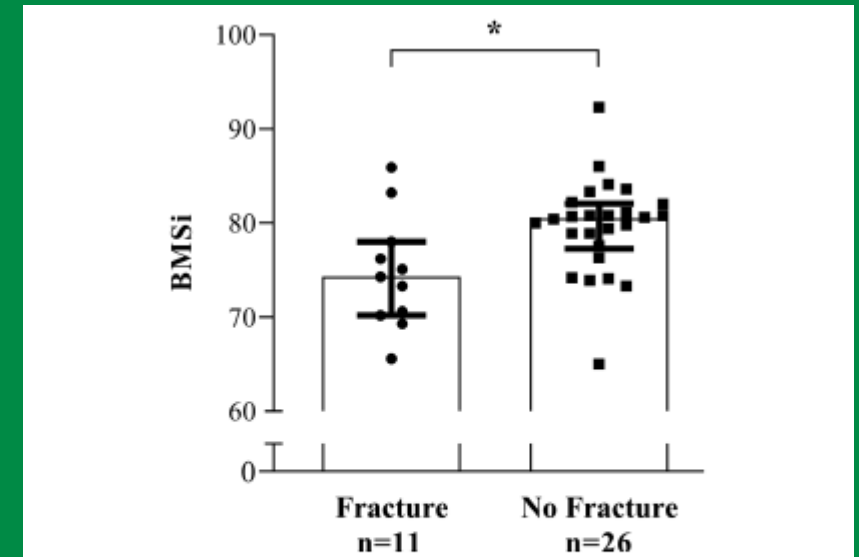


Figure 3. Bone Material Strength index (BMSi) in patients with PHPT with and without fragility fractures. Data are shown in box and whisker plots and statistical differences are displayed for BMSi. Boxes indicate median and interquartile range. Bars indicate minimum and maximum values. * $P = .015$.

Clinical Research Article

DXA-Based Bone Strain Index: A New Tool to Evaluate Bone Quality in Primary Hyperparathyroidism

Gaia Tabacco,^{1,*} Anda M Naciu,^{1,*} Carmelo Messina,^{2,3} Gianfranco Sanson,⁴ Luca Rinaudo,⁵ Roberto Cesareo,⁶ Stefania Falcone,⁷ Silvia Manfrini,¹ Nicola Napoli,¹ John P. Bilezikian,⁸ Fabio M. Ulivieri,⁹ and Andrea Palermo¹

Table 1. Baseline characteristics of the study population

Variable	n	PHPT (n = 50)	Control (n = 100)	P value
Demographic and clinical features				
Age, years	150	65.2 ± 11.6	65.2 ± 8.2	0.996
Sex, female	150	47 (94%)	95 (95%)	0.535
BMI, kg/m ²	150	27.9 ± 6.0	25.5 ± 4.4	0.011
Menopause age, years	142	50.2 ± 3.9	49.8 ± 3.1	0.517
Length of menopause, years	142	15.1 ± 9.6	15.7 ± 8.2	0.731
Biochemical analysis				
Albumin-adjusted serum total calcium, mg/dL	150	10.8 ± 0.4	9.4 ± 0.4	<0.001
Serum phosphorus, mg/dL	150	2.8 ± 0.5	3.6 ± 0.5	<0.001
PTH, pg/dL	150	143.6 ± 72.4	52.6 ± 13.7	<0.001
25-OH vitamin D, ng/mL	150	32.0 ± 7.8	31.6 ± 12.0	0.849
Serum creatinine, mg/dL	150	0.7 ± 0.2	0.7 ± 0.1	0.886
GFR, mL/min/m ²	150	88.0 ± 24.6	82.4 ± 15.5	0.146
CTX, ng/mL	50	0.5 ± 0.3	--	--
PINP, ng/mL	50	71.9 ± 41.8	--	--
Bone measures				
Vertebral fractures	150	18 (36.7%)	10 (10%)	<0.001
1/3 DR-BMD, g/cm ²	89	0.566 ± 0.07	0.625 ± 0.06	<0.001
1/3 DR Z-score	89	-0.40 ± 1.02	0.42 ± 0.83	<0.001
FN-BMD, g/cm ²	150	0.633 ± 0.112	0.666 ± 0.081	0.042
FN Z-score	150	-0.43 ± 0.99	-0.15 ± 0.81	0.070
FN-BSI	150	1.72 ± 0.41	1.49 ± 0.35	0.001
TH-BMD, g/cm ²	150	0.793 ± 0.136	0.824 ± 0.102	0.130
TH Z-score	150	-0.01 ± 1.15	0.20 ± 0.90	0.207
TH-BSI	150	1.51 ± 0.33	1.36 ± 0.25	0.002
LS-BMD, g/cm ²	150	0.869 ± 0.197	0.884 ± 0.129	0.632
LS Z-score	150	0.13 ± 1.97	0.19 ± 1.31	0.867
LS-BSI	150	2.28 ± 0.59	2.02 ± 0.43	0.009
TBS	150	1.24 ± 0.09	1.30 ± 0.10	0.001
LS T-score adjusted for TBS	150	-2.40 ± 1.05	-1.82 ± 1.02	0.002
LS Z-score adjusted for TBS	150	-0.41 ± 1.04	0.27 ± 0.99	<0.001
Osteoporosis	150	17 (34%)	17 (17%)	0.01
Osteopenia	150	29 (58%)	79 (79%)	0.003

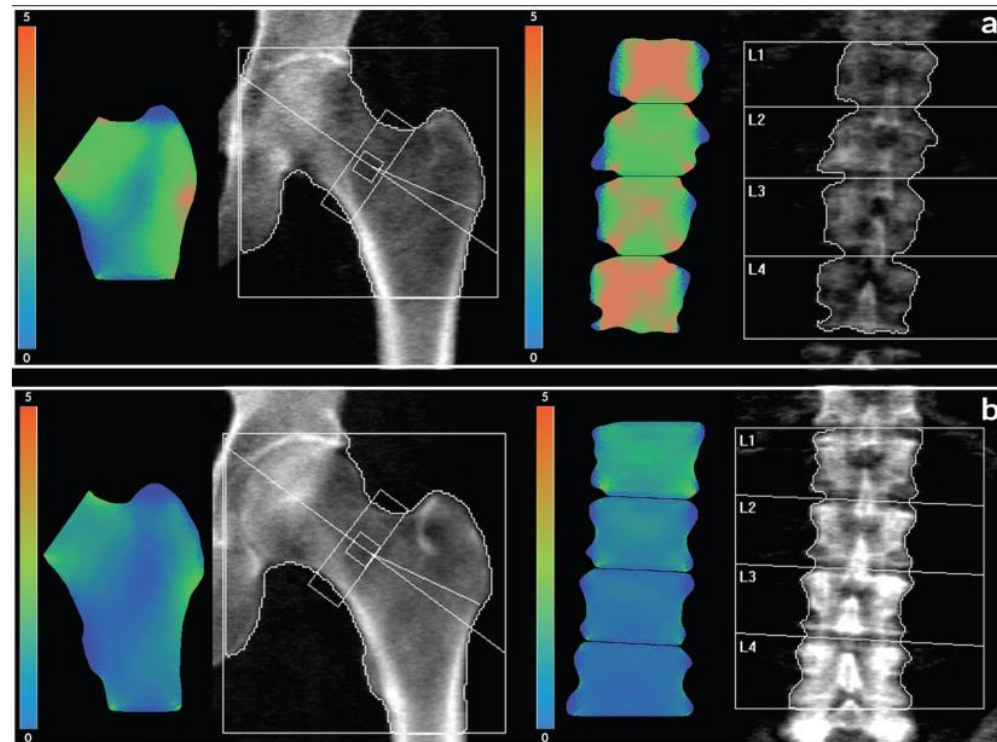


Figure 1. Femoral and lumbar spine BSI images in a subject with hyperparathyroidism (a) and in a control subject (b). The corresponding values of BSI were: a, femoral neck BSI 2.33; total hip BSI 1.94; lumbar spine BSI 3.02. b, femoral neck BSI 1.13; total hip BSI 1.17; lumbar spine BSI 0.93.

Table 2. Performance of LS-BSI to predict vertebral fractures in logistic regression models adjusted for different covariates

Model	R ²	LS-BSI ≥ 2.2 adjusted OR; 95% CI (P value)	Adjustments	AUC (95% CI); P value
# 1	0.243	6.887 (1.628-29.138); P = 0.009	Sex, Age	0.768 (0.597-0.938); P = 0.019
# 2	0.270	7.709 (1.752-33.924); P = 0.007	Sex, Age, BMI	0.795 (0.618-0.972); P = 0.009
# 3	0.376	9.602 (1.251-73.696); P = 0.030	Sex, Age, BMI, CTX, P1NP	0.825 (0.666-0.984); P = 0.004
# 4	0.189	5.739 (1.244-26.481); P = 0.025	TBS	0.735 (0.535-0.935); P = 0.039
# 5	0.251	7.152 (1.355-37.755); P = 0.020	TBS, Sex, Age, BMI	0.795 (0.616-0.974); P = 0.009
# 6	0.388	15.120 (1.059-215.786); P = 0.045	TBS, Sex, Age, BMI, CTX, P1NP	0.830 (0.676-0.984); P = 0.004

Abbreviations: AUC, area under the receiver operating characteristics curve; BMI, body mass index (kg/m²); CTX, collagen telepeptide (ng/mL); LS-BSI, lumbar spine bone strain index; P1NP, aminoterminal propeptide (ng/mL); TBS, trabecular bone score.

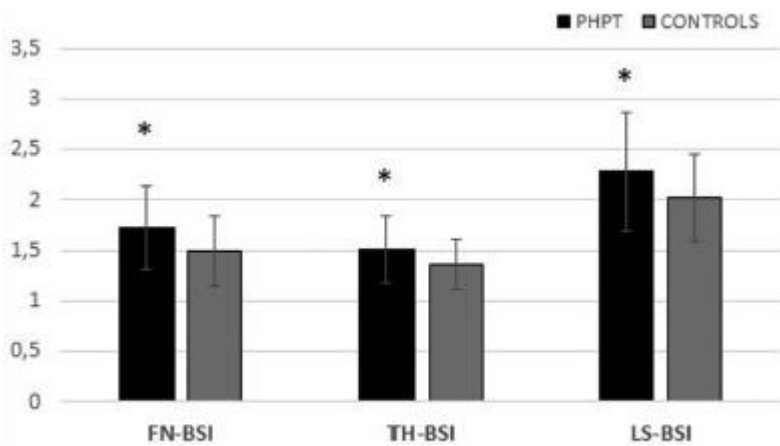


Figure 2. Evaluation of BSI in PHPT and control group. Data are presented as mean (bars) and SD (whiskers). *P < 0.01.

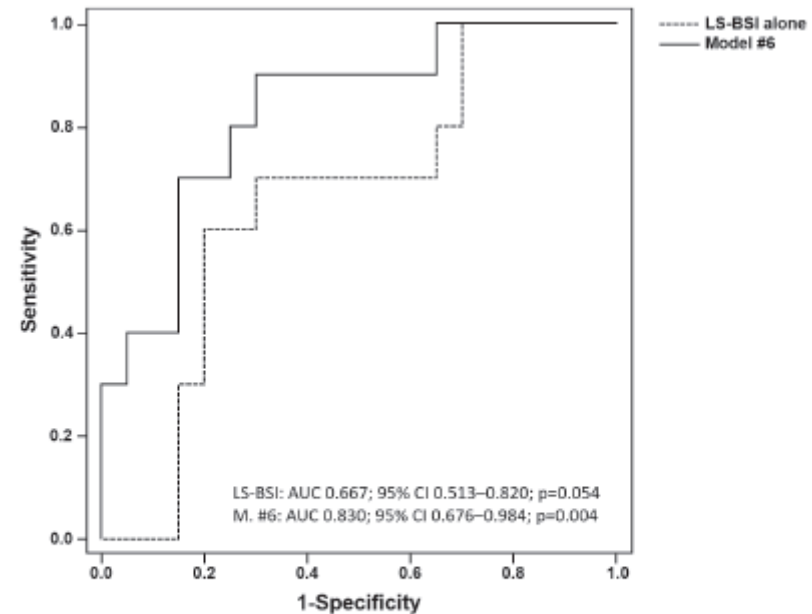


Figure 3. ROC curve of LS-BSI alone or adjusted for confounders for detecting PHPT patients with prevalent vertebral fractures. Covariates in Model #6: LS-BSI, TBS, Sex, Age, BMI, CTX, P1NP.

Risk of Fractures in PHPT

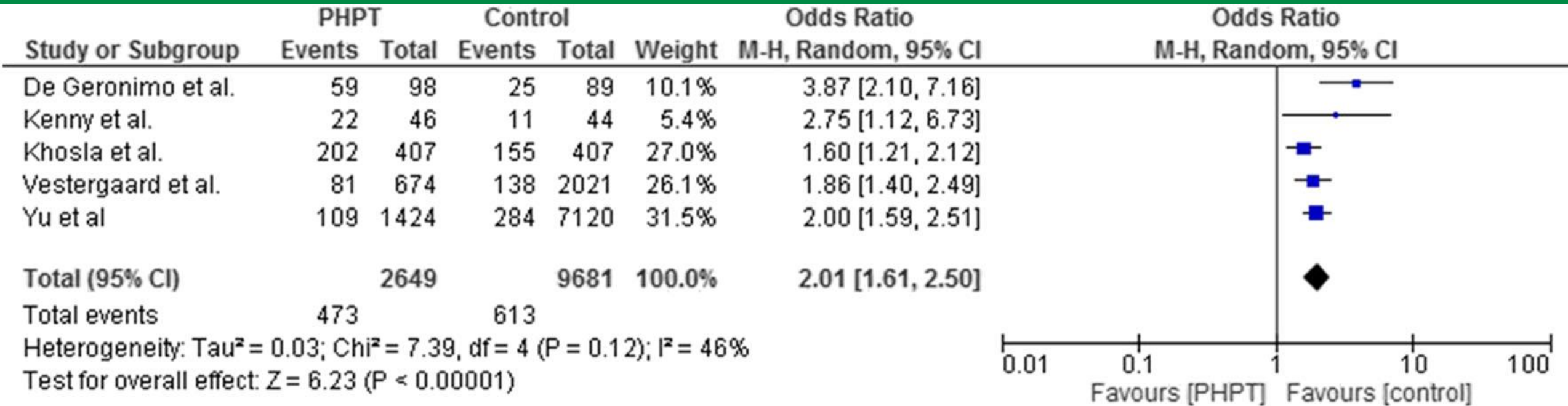


Fig. 2 Forest plot for the comparison of any fractures in patients with primary hyperparathyroidism (PHPT) compared with a control group

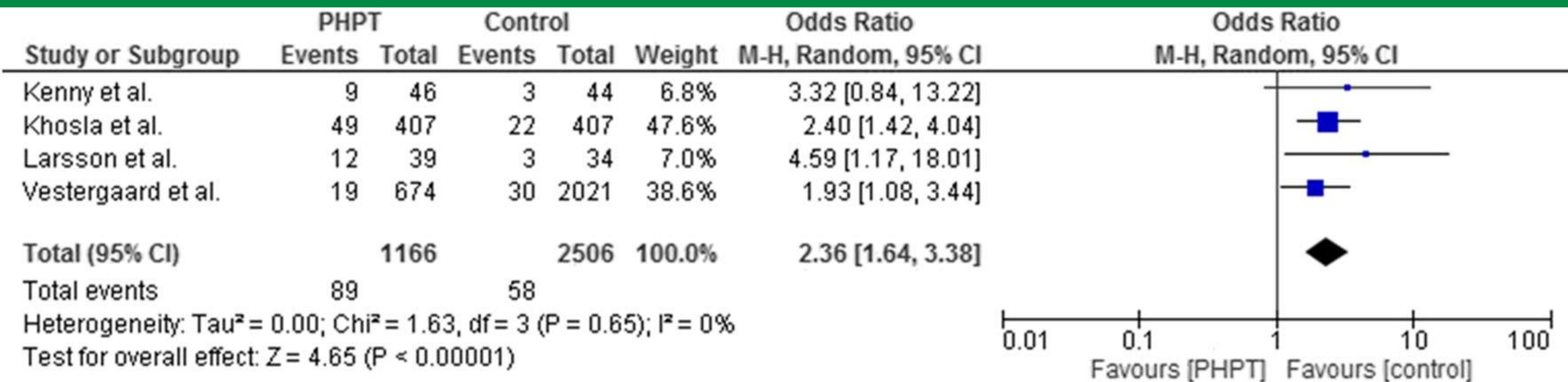


Fig. 3 Forest plot for the comparison of distal forearm fractures in patients with primary hyperparathyroidism (PHPT) compared with a control group

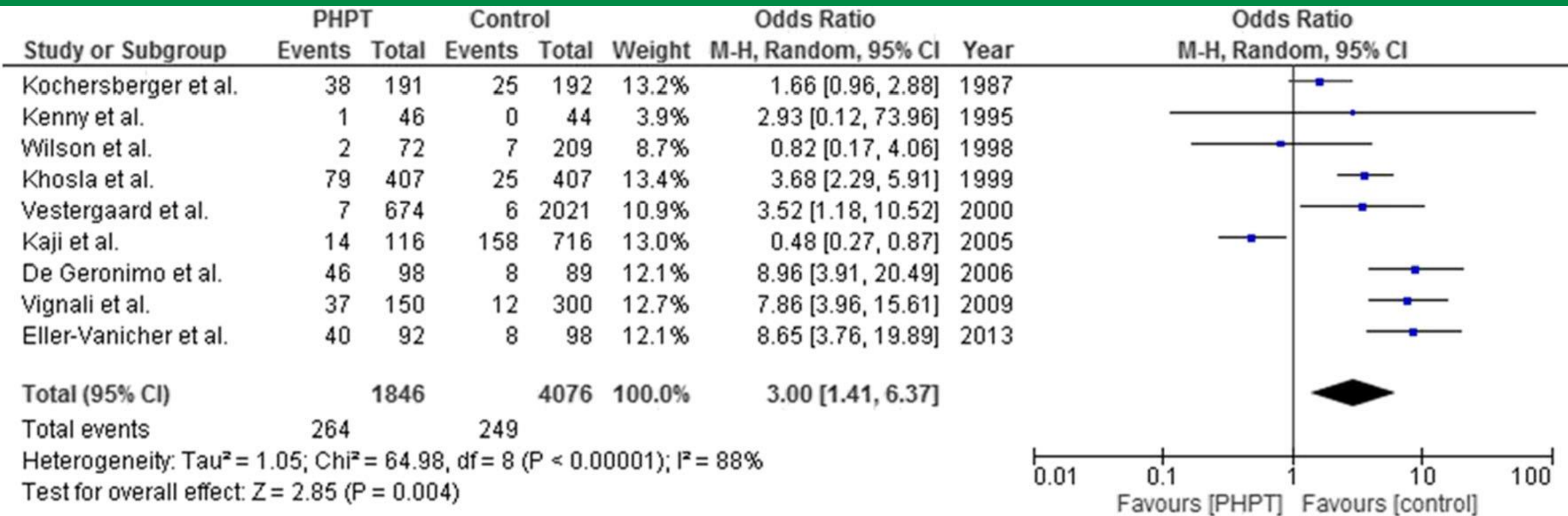
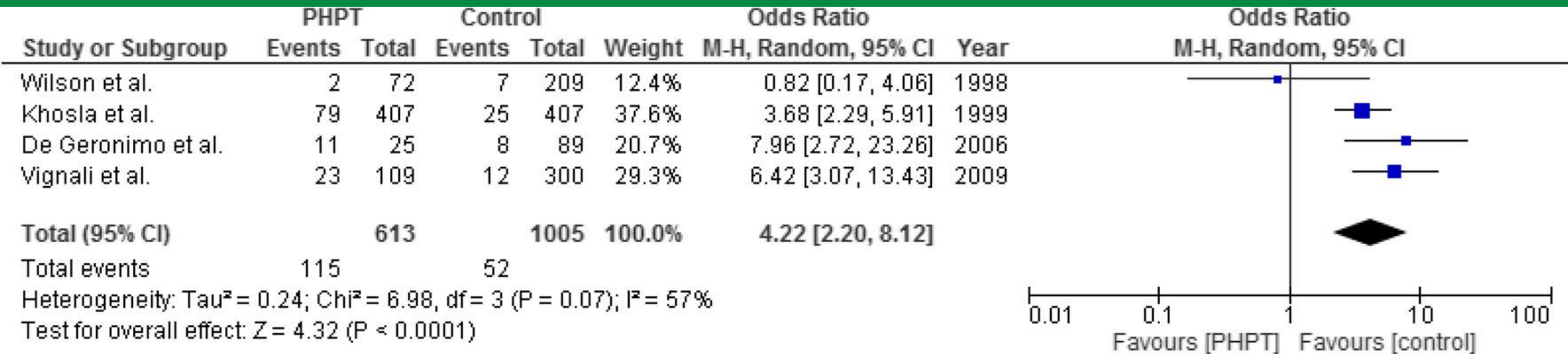


Fig. 4 Forest plot for the comparison of vertebral fracture risk in patients with primary hyperparathyroidism (PHPT) compared with a control group



Forest plot for the comparison of vertebral fracture risk in patients with mild primary hyperparathyroidism(PHPT) compared with a control group

Risk of Fracture Among Older Adults With Primary Hyperparathyroidism Receiving Parathyroidectomy vs Nonoperative Management

Characteristic	Unadjusted, No. (%)			SMD
	Overall cohort	Parathyroidectomy	Nonoperative	
Total No.	210 206	63 136	147 070	NA
Sex				
Male	44 569 (21.2)	13 684 (21.7)	30 885 (21.0)	-0.016
Female	165 637 (78.8)	49 452 (78.3)	116 185 (79.0)	0.016
Age group, y				
66-75	117 960 (56.1)	42 024 (66.6)	75 936 (51.6)	-0.307
76-85	73 491 (35.0)	19 010 (30.1)	54 481 (37.0)	0.147
≥86	18 755 (8.9)	2102 (3.3)	16 653 (11.3)	0.310
Race or ethnicity				
American Native	453 (0.2)	150 (0.2)	303 (0.2)	-0.007
Asian	1953 (0.9)	390 (0.6)	1563 (1.1)	0.049
Black	19 797 (9.4)	4741 (7.5)	15 056 (10.2)	0.096
Hispanic	2280 (1.1)	480 (0.8)	1800 (1.2)	0.047
White	183 433 (87.3)	56 888 (90.1)	126 545 (86.0)	-0.126
Unknown	2290 (1.1)	487 (0.8)	1803 (1.2)	0.046
ADI group				
Most advantaged	52 899 (25.2)	12 717 (20.1)	40 182 (27.3)	0.169
Slightly advantaged	68 471 (32.6)	20 784 (32.9)	47 687 (32.4)	-0.011
Slightly disadvantaged	65 887 (31.3)	22 093 (35.0)	43 794 (29.8)	-0.112
Most disadvantaged	22 949 (10.9)	7542 (11.9)	15 407 (10.5)	-0.047
Geography				
Urban	178 718 (85.0)	51 689 (81.9)	127 029 (86.4)	0.123
Rural	31 488 (15.0)	11 447 (18.1)	20 041 (13.6)	-0.122
Frailty				
Robust	72 794 (34.6)	24 450 (38.7)	48 344 (32.9)	-0.122
Prefrail	109 087 (51.9)	32 866 (52.1)	76 221 (51.8)	-0.006
Mildly frail	19 462 (9.3)	4041 (6.4)	15 421 (10.5)	0.147
Moderately-to-severely frail	8863 (4.2)	1779 (2.8)	7084 (4.8)	0.104
Charlson-Deyo Comorbidity Index score				
0	47 672 (22.7)	16 201 (25.7)	31 471 (21.4)	-0.101
1	46 003 (21.9)	14 515 (23.0)	31 488 (21.4)	-0.038
≥2	116 531 (55.4)	32 420 (51.3)	84 111 (57.2)	0.117
Indications for parathyroidectomy				
History of osteoporosis	91 122 (43.4)	26 247 (41.6)	64 875 (44.1)	0.051
History of kidney stones	30 470 (14.5)	11 197 (17.7)	19 273 (13.1)	-0.128
History of stage 3 CKD	20 435 (9.7)	4300 (6.8)	16 135 (11.0)	0.147
Endocrinologist care ≤6 mo of diagnosis				
Yes	98 205 (46.7)	35 546 (56.3)	62 659 (42.6)	-0.277
Fracture risk factors				
Prior fracture	19 222 (9.1)	4689 (7.4)	14 533 (9.9)	0.087
Tobacco use	9317 (4.4)	3282 (5.2)	6035 (4.1)	-0.052
Alcohol abuse disorder	1715 (0.8)	457 (0.7)	1258 (0.9)	0.015
Obesity	23 916 (11.4)	7541 (11.9)	16 375 (11.1)	-0.029

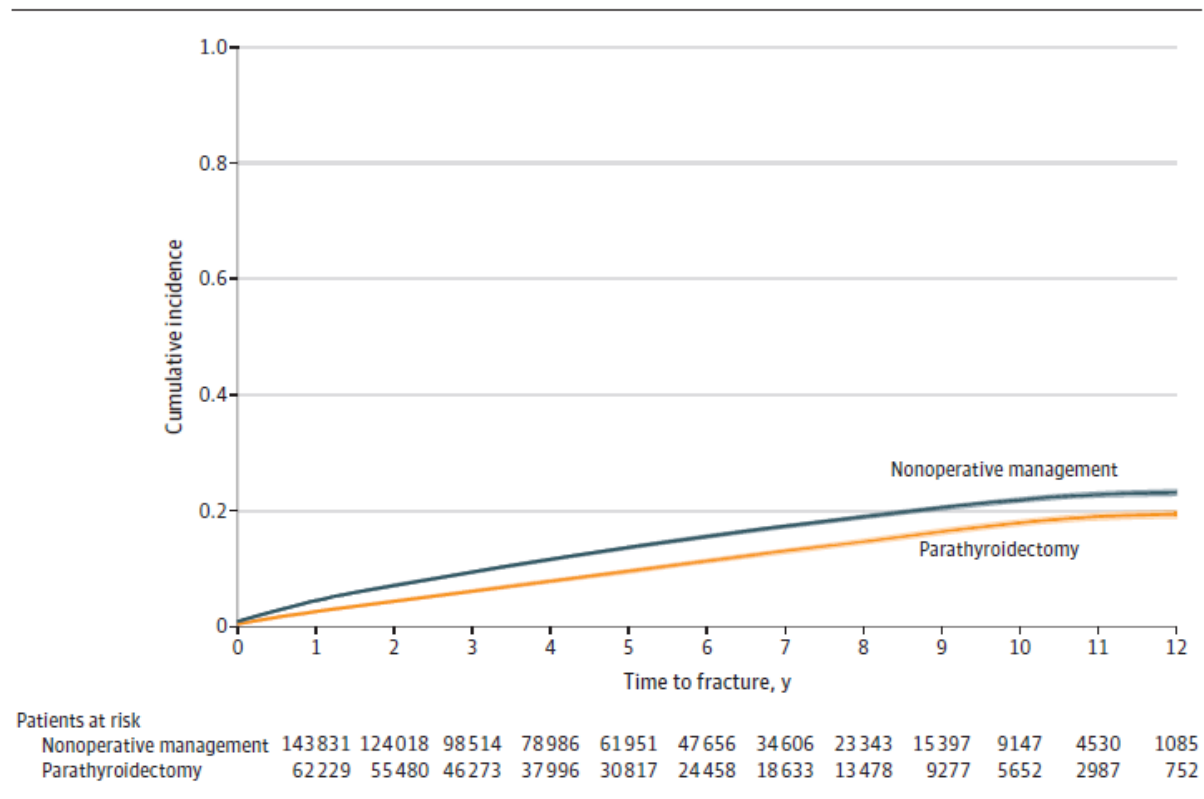
Abbreviations: ADI, area deprivation index; CKD, chronic kidney disease; IPW, inverse probability weighting. * The propensity score used for IPW was based on all characteristics listed.

Table 3. Adjusted Absolute Risk Reduction of Any Fracture and Hip Fracture Associated With Parathyroidectomy at 1, 2, 5, and 10 Years After Treatment^a

Fracture type	Time point, y	Adjusted ARR, % (95% CI)
Any fracture	1	0.67 (0.52-0.82)
	2	1.2 (1.0-1.4)
	5	2.8 (2.5-3.1)
	10	5.1 (4.6-5.5)
	10	5.1 (4.6-5.5)
Hip fracture	1	0.18 (0.11-0.26)
	2	0.36 (0.26-0.46)
	5	0.98 (0.81-1.2)
	10	2.3 (2.0-2.6)
	10	2.3 (2.0-2.6)

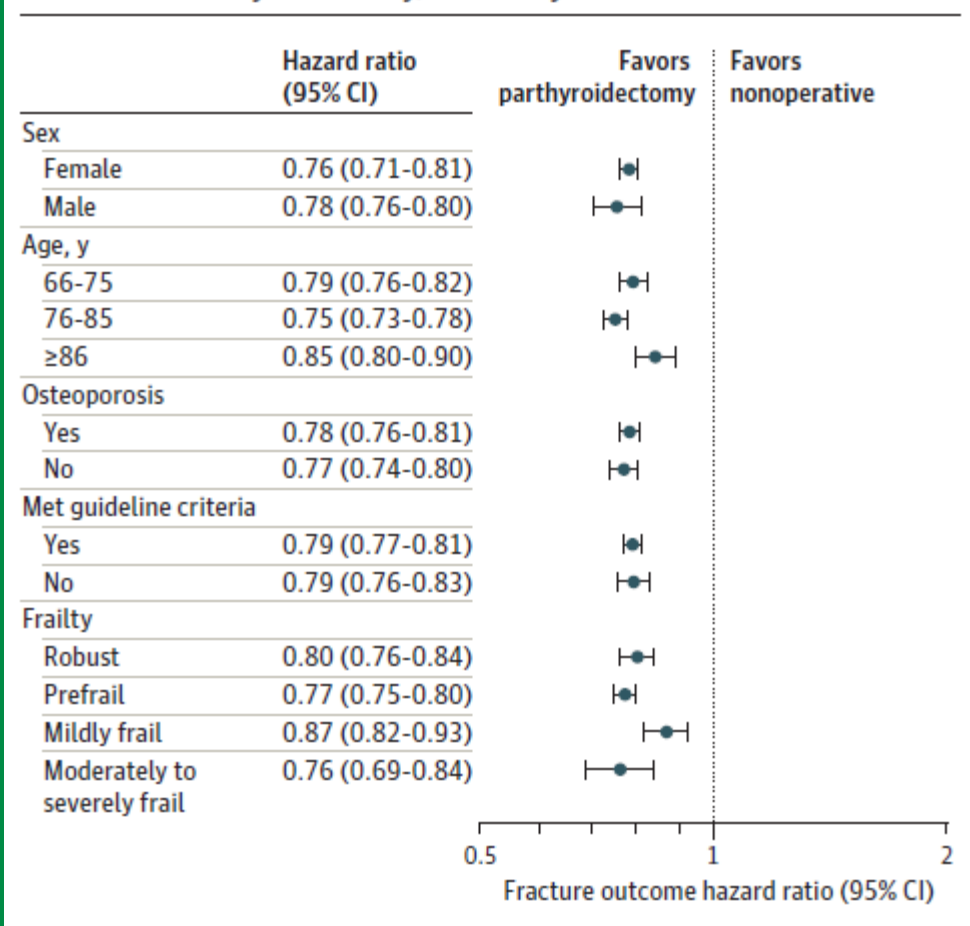
Abbreviations: ADI, area deprivation index; ARR, absolute risk reduction; PHPT, primary hyperparathyroidism.

Figure 1. Unadjusted Cumulative Incidence of Any Fracture Among Older Adults With PHPT Treated With Parathyroidectomy vs Nonoperative Management, Accounting for the Competing Risk of Death



16% lower adjusted hazard risk of any clinical Fracture and 17% lower adjusted hazard risk of hip fracture compared with those who had nonoperative management within 1 year after diagnosis

Figure 2. Adjusted HRs for the Association of Parathyroidectomy vs Nonoperative Management With Any Clinical Fracture According to Sex, Age Group, Osteoporosis History, Meeting Consensus Guideline Criteria for Parathyroidectomy, and Frailty





Clinical Research Article

Do Patients With Atypical Parathyroid Adenoma Need Close Follow-Up?

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The term *atypical parathyroid adenomas* (APAs) defines a subgroup of parathyroid tumors with **uncertain malignant potential**, characterized by some histological features shared also by PC (eg, solid growth pattern, fibrous bands, and cellular atypia) but lack unequivocal histological signs of malignancy, namely capsular, vascular, and/or perineural invasion and local invasion and/or metastasis

Table 1. Clinical, biochemical, and densitometric data of patients with atypical parathyroid adenoma enrolled in the study and comparison with control patients with parathyroid adenoma^a

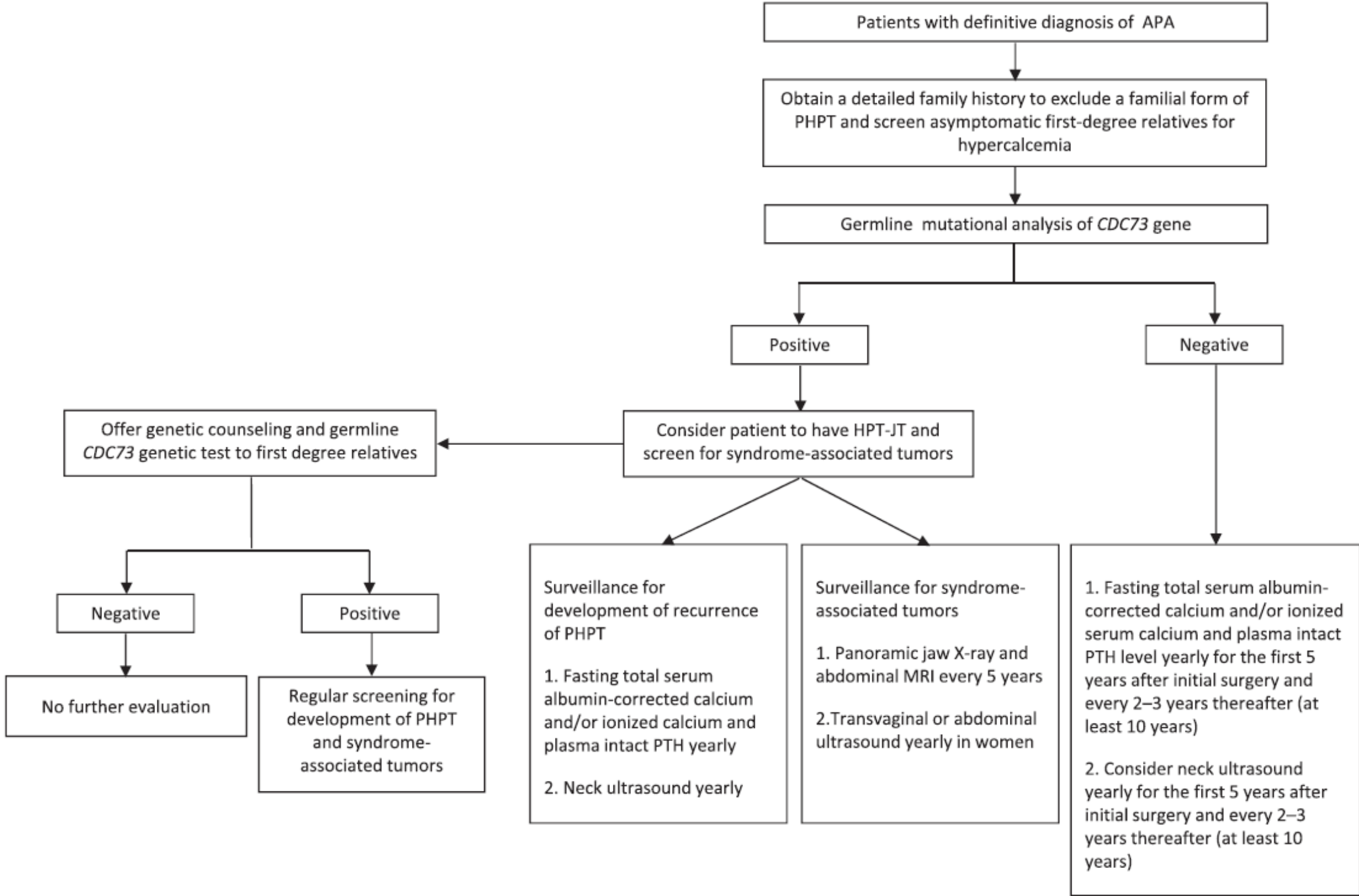
	Patients with APA				Patients with PA				Comparison between APA and PA whole groups	Comparison between symptomatic APA and symptomatic PA	Comparison between asymptomatic APA and asymptomatic PA
	Whole group (n = 58)	Symptomatic (n = 34; 59%)	Asymptomatic (n = 24; 41%)	P	Whole group (n = 57)	Symptomatic (n = 16; 28%)	Asymptomatic (n = 41; 72%)	P	P	P	P
Sex											
Female, n	37	20	17	.413	36	7		.062	1.000	.373	1.000
Males, n	21	14	7		21	9	11				
Diagnosis											
Sporadic, n	54	32	22	1.000	56	16	40	1.000	.360	.556	.285
Familial, n	4	2	2		1	0	1				
Age at diagnosis, y	56 (44-64)	56 (46-61)	58 (43-64)	.530	56 (45-64)	51 (43-60)	56 (47-64)	.280	.93	.493	.965
Clinical manifestation											
Symptomatic nephrolithiasis		20 (59%)	-			16 (100%)	-			.005	
Clinical fractures		6 (18%)	-			1 (4%)	-			.406	
Hypercalcemic crisis		5 (15%)	-			0 (0%)	-			.163	
Pancreatitis		2 (6%)	-			0 (0%)	-			.556	
Palpable neck mass	2 (3.4%)	1 (3%)	1 (4%)		1 (1.7%)	1 (4%)	-		.09	1.000	.410
Serum calcium (8.6-10.2 mg/dL) ^b	12.3 ± 2.6	12.8 ± 3.1	11.5 ± 1.2	.048	11.1 ± 0.8	11.3 ± 0.8	11 ± 0.8	.211	< .001	0.008	.105
Plasma intact PTH											
Second-generation assay (15-65 ng/mL) ^b	238 (181-927)	220 (184-845)	238 (135-913)	0.625	-	-	-				
Third-generation assay (8-40 pg/mL) ^b	141 (66-192)	204 (151-249)	65 (56-139)	.008	72 (59-104)	76 (58-102)	70 (59-110)	.989	.007	< .001	.890
Serum 25(OH)D (> 20 ng/mL) ^b (n = 42)	20.7 ± 19.1	15.8 ± 8.4	26.1 ± 25.5	.083	28 ± 10.1	24.5 ± 7.9	29.6 ± 10.7	.084	< .001	.005	.016
Creatinine (0.5-0.9 mg/dL) ^b (n = 40)	0.98 ± 0.62	0.86 ± 0.45	0.96 ± 1.09	.189	0.84 ± 0.25	1.0 ± 0.34	0.80 ± 0.19	.027	.78	.938	.610
eGFR ^c (> 60 mL/min/1.73 m ²) ^b (n = 40)	88 ± 33	91 ± 29	86 ± 37	.465	89 ± 22	88 ± 26	90 ± 21	.330	.94	.827	0.628

Table 1. Continued

	Patients with APA				Patients with PA				Comparison between APA and PA whole groups	Comparison between symptomatic APA and symptomatic PA	Comparison between asymptomatic APA and asymptomatic PA
	Whole group (n = 58)	Symptomatic (n = 34; 59%)	Asymptomatic (n = 24; 41%)	P	Whole group (n = 57)	Symptomatic (n = 16; 28%)	Asymptomatic (n = 41; 72%)	P	P	P	P
24-h urinary calcium (n = 37) (100-321 mg/24-h) ^b	398 ± 182	377 ± 188	435 ± 172	.350	353 ± 187	416 ± 183	323 ± 184	.030	.15	.348	0.007
Lumbar spine (APA, n = 48; PA n = 56)											
BMD, g/cm ²	0.82 ± 0.17	0.45 ± 0.18	0.79 ± 0.15	.221	0.85 ± 0.14	0.86 ± 0.10	0.84 ± 0.16	.631	.400	.180	.837
T score	-2.58 ± 1.09	-2.9 ± 0.93	-2.21 ± 1.12	.361	-2.25 ± 1.32	-2.06 ± 0.87	-2.31 ± 1.44	.431	.821	.685	0.702
(APA, n = 34; PA, n = 38)											
Z score (APA, n = 14; PA n = 18)	-0.61 ± 2.76	-0.95 ± 1.98	-1.04 ± 0.79	.858	-0.72 ± 1.13	-1.58 ± 0.89	-0.29 ± 0.99	.044	.816	.142	.385
Femoral neck (APA, n = 44; PA n = 56)											
BMD, g/cm ²	0.65 ± 0.17	0.63 ± 0.18	0.68 ± 0.14	.307	0.75 ± 0.75	0.99 ± 1.38	0.65 ± 0.15	.526	.660	.150	.312
T score (APA, n = 32; PA n = 38)	-2.28 ± 1.00	-2.1 ± 0.71	-1.57 ± 1.09	.244	-2.00 ± 1.24	-2.16 ± 0.94	-1.95 ± 1.32	.859	.759	.635	.096
Z score (APA, n = 12; PA n = 18)	-1.00 ± 1.84	-0.9 ± 2.06	1.18 ± 1.57	.332	-1.16 ± 0.55	-1.33 ± 0.40	-1.06 ± 0.62	.539	.826	.900	.848
1/3 distal radius (APA, n = 41; PA n = 52)											
BMD, g/cm ²	0.47 ± 0.45	0.52 ± 0.13	0.41 ± 0.67	.265	0.61 ± 0.11	0.58 ± 0.12	0.62 ± 0.11	.299	.017	.254	.217
T score (APA, n = 30; PA n = 34)	-3.57 ± 1.93	-4.24 ± 1.91	-2.85 ± 1.74	.119	-2.42 ± 1.82	-3.47 ± 2.43	-2.16 ± 1.57	.210	.029	.892	.087
Z score (APA, n = 11; PA n = 16)	-1.94 ± 2.69	-2.14 ± 3.33	-1.00 ± 2.14	.068	-0.59 ± 1.51	-1.76 ± 0.89	-0.06 ± 1.45	.015	.356	1.000	.528

Table 3. Clinical, biochemical, and pathological data of patients with persistent or recurrent disease

Pa-tient ID	Familial disease	Age at diagnosis, y/Sex	Symptoms at diagnosis	Associated diseases	Pre-PTx calcium levels, mg/dL ^a	Pre-PTx PTH levels, pg/mL	Glands removed at first surgery/histology	P/R, time to recurrence, mo	Glands removed at second surgery/histology	P/R after second surgery, time to recurrence, mo	Glands removed at third surgery/histology	Follow-up after last surgery, mo/Outcome
15	Yes (FIHP)	14/F	Nephrolithiasis, osteitis fibrosa cystica, fractures	Hodgkin lymphoma	17.2	1600 ^b	Inferior right/atypical adenoma	R (204)	Superior left/adenoma	R (31)	Inferior left/adenoma	1/Cured
420	No	20/M	Hypercalcemic crisis	None	12.7	579 ^b	Inferior left/atypical adenoma	P	–	–	–	199/Persistence
867	No	29/M	Nephrolithiasis	None	13.1	1391 ^b	Superior left and right/hyperplasia Inferior right/atypical adenoma	P	Inferior left/atypical adenoma	–	–	66/Hypoparathyroidism
1061	No	56/F	Nephrolithiasis	Nonfunctioning bilateral adrenal adenomas	12.6	199 ^c	Superior left/atypical adenoma	P	–	–	–	117/Persistence
1062	No	82/M	Nephrolithiasis	Papillary thyroid microcarcinoma Multiple lipomas	15.9	453 ^d	Superior right/atypical adenoma	P	–	–	–	67/Persistence
1086	No	41/M	Neuropsychiatric, hypercalcemic crisis, pancreatitis	Nonfunctioning adrenal adenoma	23	1634 ^b	Superior right/atypical adenoma	R (68)	Paratracheal and paraesophageal right lesion/Nest of parathyroid cells with no signs of atypia. Capsular and vascular invasion.	R (21)	–	23/Recurrence



Αντιμετώπιση

- Χειρουργική
 - Αμφω Διερεύνηση Τραχήλου (BNE)
 - negative/discordant localization imaging
 - known bilateral/multi-gland disease
 - known genetic/familial risk factors for multi-gland disease
 - those on provocative medications (e.g., lithium).
 - Minimally Invasive Parathyroidectomy (MIP)
- Συντηρητική
 - Γενικά Μέτρα
 - Διφωσφονικά / Dmab
 - Calcimimetics

TABLE 2 Guidelines for the management of ‘asymptomatic’ primary hyperparathyroidism

Strongly advise surgery	Advise/consider surgery	Nonsurgical management
<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Life expectancy <5 years • OR • Prohibitive anaesthetic risk • OR • Hostile neck (e.g., previous neck surgery, irradiation, morbid obesity)

An approach to a patient with primary hyperparathyroidism and a suspected ectopic parathyroid adenoma

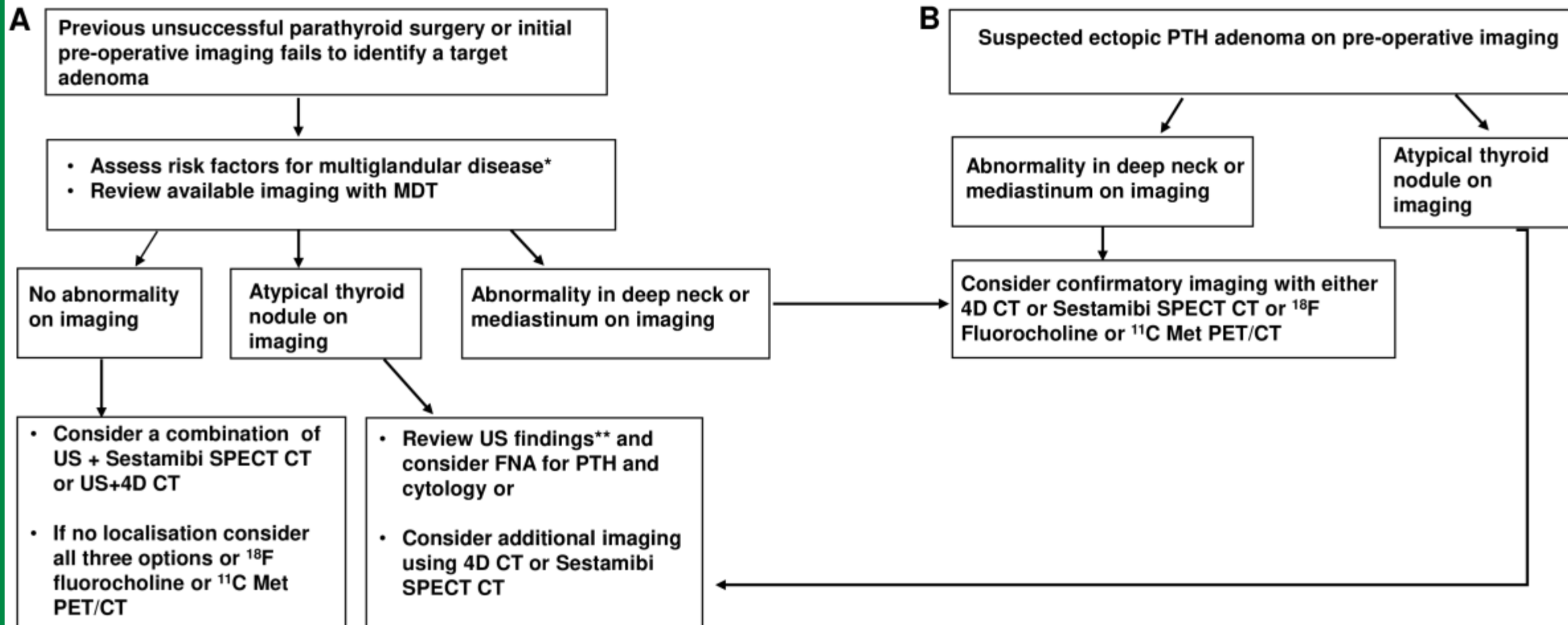
Glasgow C, et al JCEM 2022, in press

- Incidence of ectopic parath glands: 10-22%
- In repeat surg: 28-49%

Inferior parathyroid		Superior parathyroid	
<input type="checkbox"/> Thymus	31-38%	<input type="checkbox"/> Retroesophageal	2-58%
<input type="checkbox"/> Thyro-thymic ligament	31%	<input type="checkbox"/> Retropharyngeal	17%
<input type="checkbox"/> Posterior mediastinum	7%	<input type="checkbox"/> Tracheoesophageal	16%
<input type="checkbox"/> Aorto-pulmonary window	4%	<input type="checkbox"/> Posterior superior mediastinum	5%
<input type="checkbox"/> Intrathyroidal	13%	<input type="checkbox"/> Submandibular	5-8%
		<input type="checkbox"/> Carotid sheath	3-9%
		<input type="checkbox"/> Intrathyroidal	3%
		Intrathyroidal (not specified if superior or inferior parathyroid gland)	4-18%
Rare locations			
<input type="checkbox"/> carotid bifurcation , <input type="checkbox"/> hypoglossal nerve, <input type="checkbox"/> vagus nerve, <input type="checkbox"/> pericardium, <input type="checkbox"/> Right dome of the diaphragm, <input type="checkbox"/> Supraclavicular region, <input type="checkbox"/> Piriform sinus, <input type="checkbox"/> Soft palate			

Imaging modality	Key features
Ultrasound	<ul style="list-style-type: none"> <input type="checkbox"/> Inexpensive, operator dependant <input type="checkbox"/> Poor sensitivity for identification of ectopic glands in the mediastinum or paraesophageal areas <input type="checkbox"/> Sensitivity affected in patients with coexistent thyroid disease or elevated BMI <input type="checkbox"/> Features that help distinguish between intrathyroidal adenoma and thyroid nodule include; a solid composition, profound hypoechogenicity, peripheral distribution of vascularity, presence of feeding polar vessel
Ultrasound guided FNA	<ul style="list-style-type: none"> <input type="checkbox"/> Allows preoperative confirmation of an intrathyroidal or retrothyroidal adenoma <input type="checkbox"/> May be difficult to differentiate a parathyroid adenoma from thyroid nodule based on cytology alone <input type="checkbox"/> High sensitivity (82-84%) and specificity (100%) for identifying parathyroid tissue using PTH measurements from FNA biopsy needle washings <input type="checkbox"/> Risk of tumour seeding in parathyroid carcinoma
Parathyroid scintigraphy	<ul style="list-style-type: none"> <input type="checkbox"/> Sensitivity of 89% and positive predictive value of 90% for localizing ectopic glands <input type="checkbox"/> SPECT/CT may provide more precise anatomical localisation compared to SPECT <input type="checkbox"/> Parathyroid uptake can be masked by sestamibi concentration in thyroid or submandibular glands
4D CT	<ul style="list-style-type: none"> <input type="checkbox"/> More sensitive for smaller lesions compared to scintigraphy (4mm vs 10mm respectively) <input type="checkbox"/> May identify lesions in carotid sheath, retro-oesophageal and mediastinal spaces
PET radiotracers	<ul style="list-style-type: none"> <input type="checkbox"/> Met-PET/CT and 18F-Fluorocholine PET/CT can be used to detect ectopic parathyroid adenomas and may be more sensitive than sestamibi SPECT/CT <input type="checkbox"/> Limited to specialist centers
Selective venous sampling	<ul style="list-style-type: none"> <input type="checkbox"/> Invasive

Proposed approach to localizing a suspected ectopic parathyroid adenoma in patients with primary hyperparathyroidism



*= risk factors for multiglandular PTH disease such as ; hereditary PHPT, lithium therapy, radiotherapy or severe vitamin D deficiency

**= features suggestive of an intrathyroidal parathyroid adenoma such as ; solid composition, hypoechoogenicity, presence of a feeding polar vessel

Diagnosis of PHPT

Symptomatic PHPT

Asymptomatic PHPT

- ≥ 1 of the parameters below:
1. Serum Ca >1.0 mg/dL from the upper normal level
 2. eGFR < 60 ml/min,
 3. Nephrolithiasis, nephrocalcinosis or 24h urine Ca >400 mg/24h and abnormal nephrolithiasis profile
 4. T-score ≤ -2.5 (any skeletal site) and/or osteoporotic fracture
 5. Age ≤ 50 years

Cinacalcet

Surgery

YES

NO

Follow up

Pharmaceutical treatment

- ≥ 1 from the parameters below:
1. Serum Ca >1.0 mg/dL from the upper normal level
 2. eGFR < 60 ml/min,
 3. Nephrolithiasis, nephrocalcinosis
 4. T-score ≤ -2.5 (any skeletal site) or ≤ -2.0 and annual decrease of BMD above the Least Significant Change
 5. Osteoporotic fracture

