MAYO CLINIC

BIOCHEMICAL EVALUATION OF HYPERPARATHYROIDISM: WHAT TO ORDER AND HOW TO INTERPRET THE RESULTS

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DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INDUSTRY

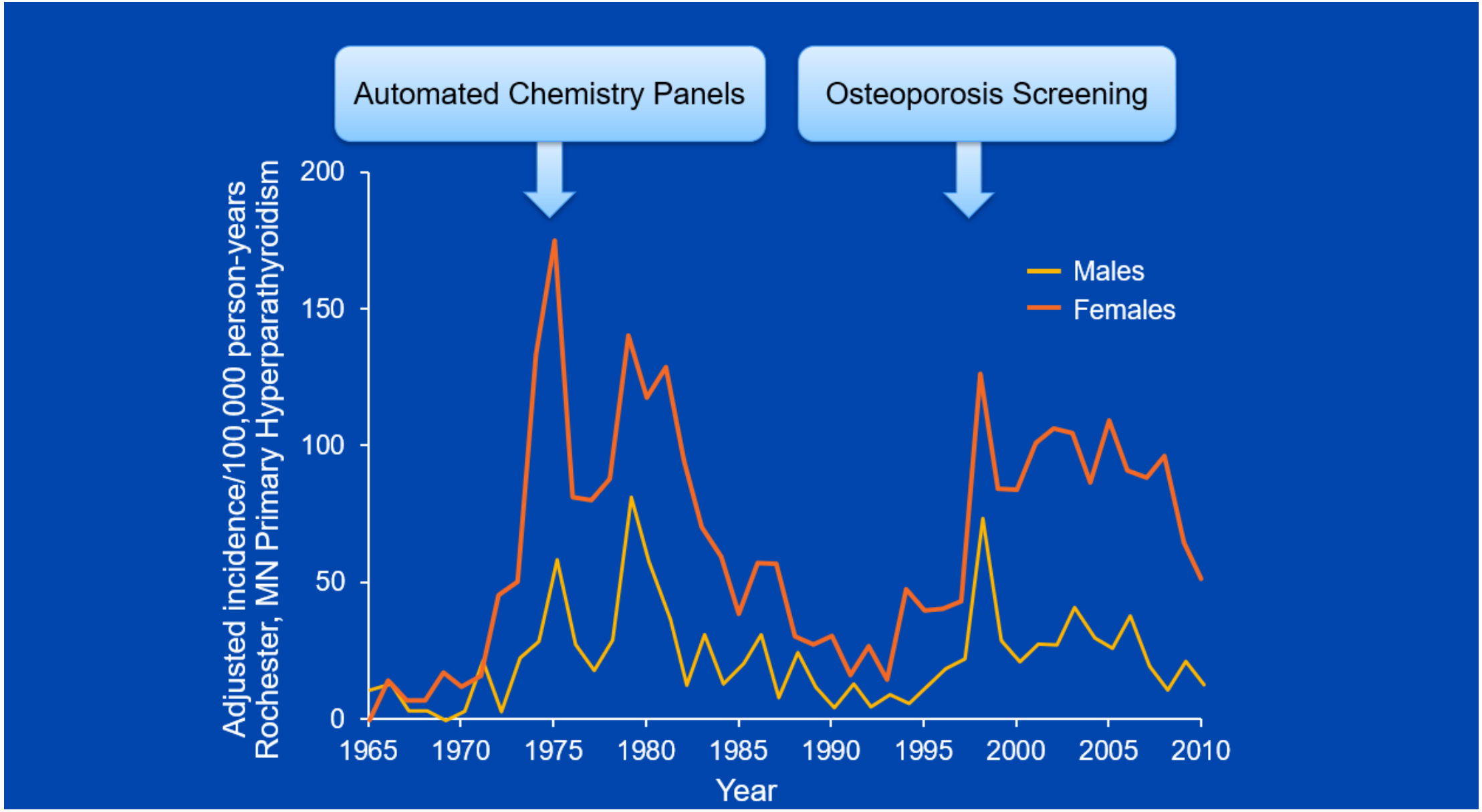
- Nothing to disclose

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Nothing to disclose

LEARNING OBJECTIVES

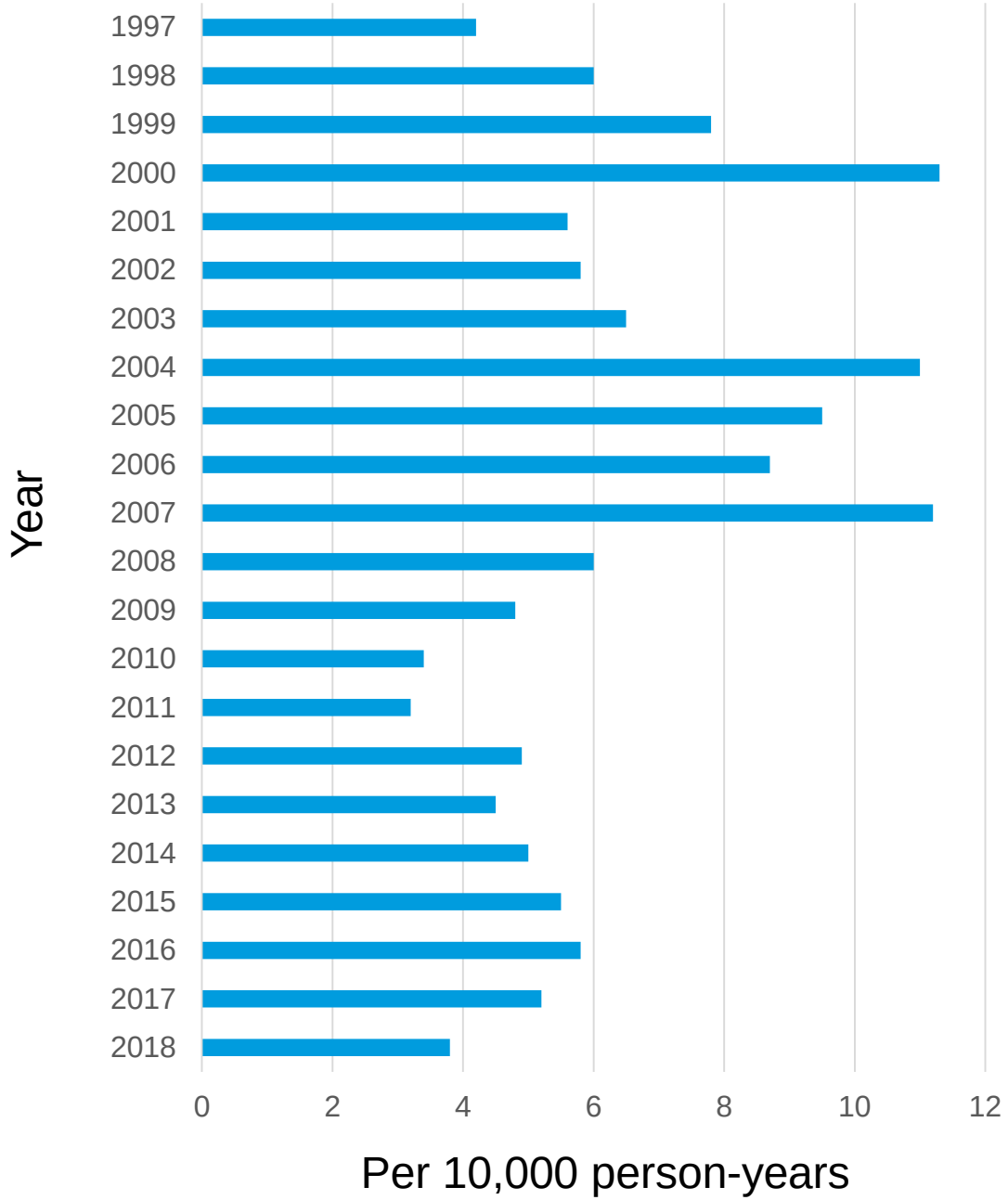
- Recognize unique subsets of PHPT and secondary HPT
- Evaluate patients with elevated PTH and normal serum calcium levels
- Understand the natural history of serum calcium and PTH in the general population and after parathyroidectomy



Greibeler ML et al. Bone 2015;73:1

PHPT INCIDENCE RATES

TAYSIDE, SCOTLAND, UK



None of these include patients with normocalcemia PHPT

Redrawn from: Soto-Pedre E et al. J Clin Endocrinol Metab 2023

PRIMARY HYPERPARATHYROIDISM
CLASSICAL LABORATORY RESULTS

- PTH
  - Normal (20%) or elevated (80%)
  - Normal = usually upper 1/2 to 1/3 of reference range
- Phosphorus
  - Low in 25% in referral populations
- Calcium creatinine clearance ratio
  - $(U_{Ca}xS_{Cr})/(S_{Ca}xU_{Cr}) < 0.01$ suggests FBHH
  - >0.02 essentially rules our FBHH
- 25-D low in 50% – worse PHPT if severe

PHPT SUBTYPES

- Classic
- Mild PHPT
  - Normoparathyroid PHPT
  - Normocalcemia PHPT
- Thiazide-associated PHPT
- Hypercalciuric PHPT
- Lithium-associated PHPT
- Familial (genetic) PHPT
- Recurrent PHPT
- Persistent PHPT

NORMOCALCEMIC PRIMARY HYPERPARATHYROIDISM

Rochester Serum Calcium

Total Calcium Results MCR (2 years)					
	0-11m	1-17	18-59	60-90	91+
Average	9.94	9.42	9.19	9.18	9.05
Median	10.00	9.50	9.30	9.20	9.10
SD	1.39	0.73	0.70	0.73	0.76

Reference range for Mayo Enterprise

0-11 months: 8.7-11.0 mg/dL (2.18 – 2.75 mmol/L)
1-17 years: 9.3-10.6 mg/dL (2.33 – 2.65 mmol/L)
18-59 years: 8.6-10.0 mg/dL (2.15 – 2.5 mmol/L)
≥ 60 years: 8.8-10.2 mg/dL (2.2– 2.55 mmol/L)

CLINICAL CHARACTERISTICS OF THE OPRA STUDY COHORT AT BASELINE AND FOLLOW-UP VISITS

Characteristic	Age 75 yr (n=999)	Age 80 yr (n=693)	Age 85 yr (n=348)
Serum PTH (pmol/L)	**4.7±2.1**	**5.1±2.7**	**5.2±4.2**
Normal PTH (1.6 to 6.9 pmol/L), No., (%)	877 (88%)	512 (74%)	266 (76%)
Low PTH (1.6 pmol/L), No., (%)	13 (1%)	47 (7%)	16 (5%)
High PTH (>6.9 pmol/L), No., (%)	**109 (11%)**	**134 (19%)**	**66 (19%)**
Serum 250HD (nmol/L)	62±19	78±30	79±26
eGFR* (mL/min/1.73m^2)	**68±15**	**61±14**	**53±14**
Serum calcium (mmol/L)	2.4±0.1	2.4±0.1	2.3±.01
Serum phosphate (mmol/L)	1.1±0.2	1.1±0.1	1.1±0.1
Height (cm)	160±6	159±6	158±6
Weight (kg)	68±12	66±12	64±11
BMI (kg/m^2)	26±4	26±4	25±4

*eGFR based on cystatin C and creatinine

Buchebner D et al. J End Soc 2017

SUMMARY

- Serum calcium levels are relatively stable with aging in healthy adults
- PTH increases with aging in older adults and is related to reduction in renal function and lower 25-hydroxyvitamin D levels
- PTH is high in 11% of 75-year-olds and 19% of ≥ 80-85-year-olds
  - Is this normocalcemic PHPT?
  - Should we adjust reference range for age?
- PTH results can vary depending on measurement platform utilized

NORMOCALCEMIC PHPT

- Persistently normal albumin-adjusted serum calcium and ionized calcium with elevated PTH on at least 2 consecutive measures without secondary cause (disease or drugs) of elevated PTH over 3 - 6 months
  - 25-D ≥ 30 ng/mL (> 74 nmol/L)

Bilezikian JP et al. J Bone Miner Res 2022;37;2293-2314

CASE 1

CASE 1

- 67-year-old referred for hyperparathyroidism with normal serum calcium
- Diagnosed with osteoporosis on screening BMD 1 year prior
  - Calcium - 9.1 mg/dL, PTH -170 pg/mL, normal 25(OH)D, and normal serum creatinine with eGFR
  - 24-hour urine calcium undetectable
- Parathyroid scan and neck ultrasound nonlocalizing but showed 1.5 X 1.1 X 1.2 TIRADS 4 right thyroid nodule (FNA benign)

CASE 1 (CONTINUED)

- No family history of PHPT
- No lithium or HCTZ use
- No prior GI/weight loss surgeries
- Denies weight changes and tends toward constipation otherwise asymptomatic
- Taking vitamin D3 2000 ID daily and an estimated 1700 mg of daily calcium between diet and supplements
- Zoledronic acid 5 mg administered 8 months ago
- Most recent lab after zoledronic acid
  - Calcium 8.4 mg/dL, phosphorus 3.6 mg/dL, PTH 254 pg/mL and 25(OH)D 26 ng/mL

MEDICATIONS

- Vitamin D3 2000 ID daily
- Estimated 1700 mg of daily calcium between diet and supplements
- Zoledronic acid 5 mg administered 8 months ago
- Colace 100 mg daily
- Oral probiotic
- Multivitamin
- Cetirizine 10 mg daily

Lowers serum calcium	Lowers PTH	Increases serum calcium	Increases PTH
Denosumab	Calcium	Lithium	Estrogen replacement
Potent IV bisphosphonates	Vitamin D	PTH analogues	Potent IV bisphosphonates
Ferric carboxymaltose	Aromatase inhibitors	Thiazide diuretics	Loop diuretics
Estrogen replacement (in primary hyperparathyroidism)	Renin-angiotensin-aldosterone inhibitors	Denosumab discontinuation	Calcium channel blockers
Raloxifene (in primary hyperparathyroidism)	Cinacalcet		Ferric carboxymaltose
Romosozumab			Tenofovir
Cinacalcet			Denosumab
Calcitonin			Romosozumab
Glucocorticoids (with concomitant hypovitaminosis D)			Calcitonin
			SGLT2 inhibitors
			Phenytoin/phenobarbital
			Lithium

LOWER THAN EXPECTED PTH IN PHPT

Interfering factor	Clinical Considerations
Physiologic factors	Calcium, vitamin D, pH, volume status
Second contributing non-PTH cause of hypercalcemia (multifactorial)	Sarcoidosis, hyperthyroidism, CKD, etc.
Hook effect	Serial sample dilution
Heterophile antibodies	Serial sample dilution/use different lab
Atypical bioactive PTH	Serial sample dilution
General assay interference	
Extremely high lipids/protein	Hinder analyte binding to assay antibodies
High concentration of optically active substance (bilirubin/hemoglobin)	Interfere with signal detection
High biotin levels	In assays that use biotin-streptavidin binding to capture the capture antibody onto a solid support before signal read-out
Anti-streptavidin antibodies in patients serum	

Immunoassay Test	Biotin Interference
T3/FT3	Falsely ↑
FT4/T4	Falsely ↑
TSH	Falsely ↓
Thyroglobulin	Falsely ↓
Thyroglobulin Ab	Falsely ↓
Estradiol Rapid	Falsely ↑
Progesterone	Falsely ↑
Prolactin	Falsely ↓
Macroprolactin	Falsely ↓
C-Peptide	Falsely ↓
Insulin	Falsely ↓
PTH	Falsely ↓
Osteocalcin	Falsely ↓
Beta CrossLaps	Falsely ↓

Instruct patients to hold biotin supplements for at least 12 hours prior to blood collection

PHYSICAL EXAM

- HT – 161.2 cm; WT – 66.2 kg; BMI – 25.48
- Unremarkable

WHAT IS YOUR DIAGNOSIS?

A. Normocalcemic PHPT

B. Secondary HPT due to zoledronic acid

C. Secondary HPT due to malabsorption

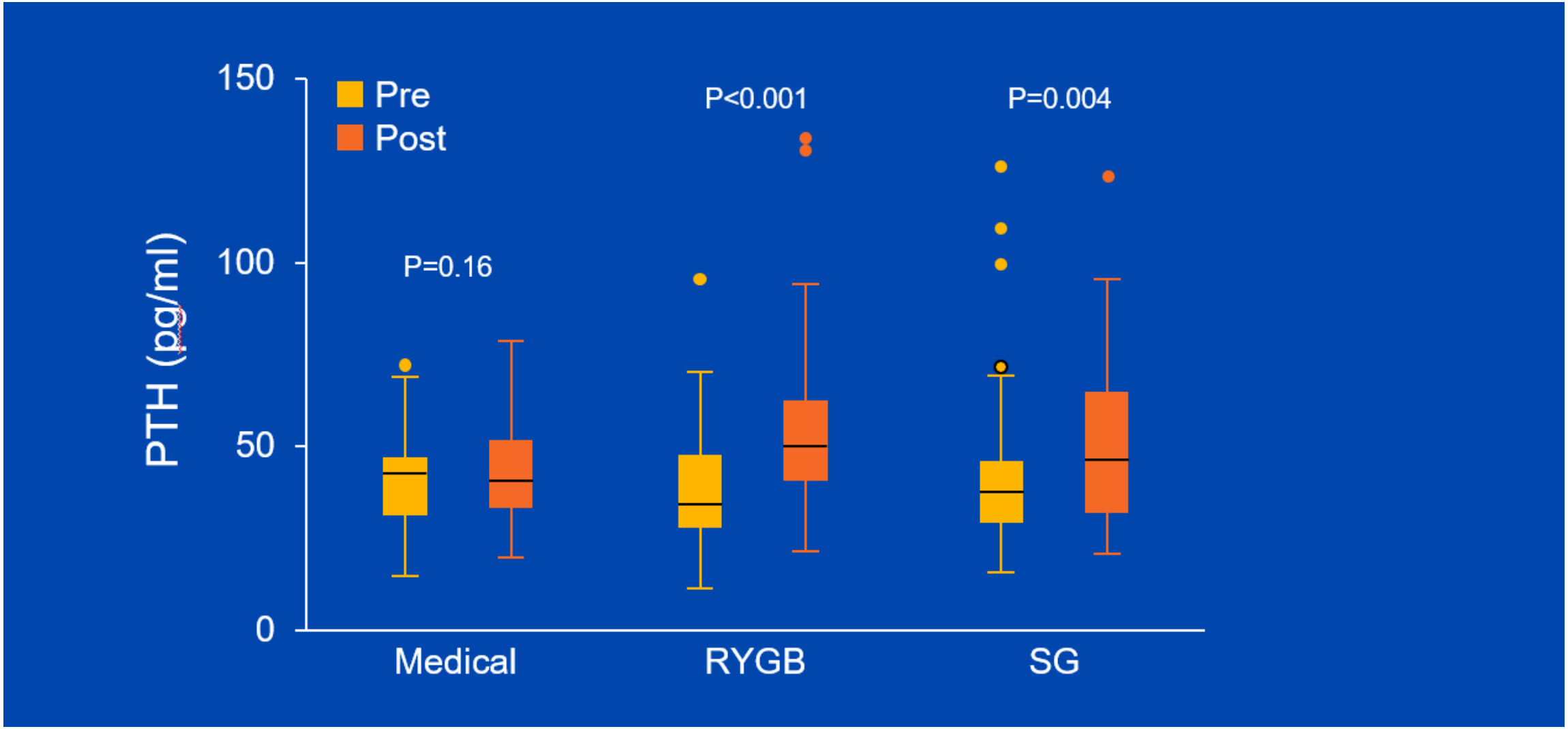
D. Inaccurate PTH due to interfering factor

E. Age appropriate PTH

MAYO TEST RESULTS

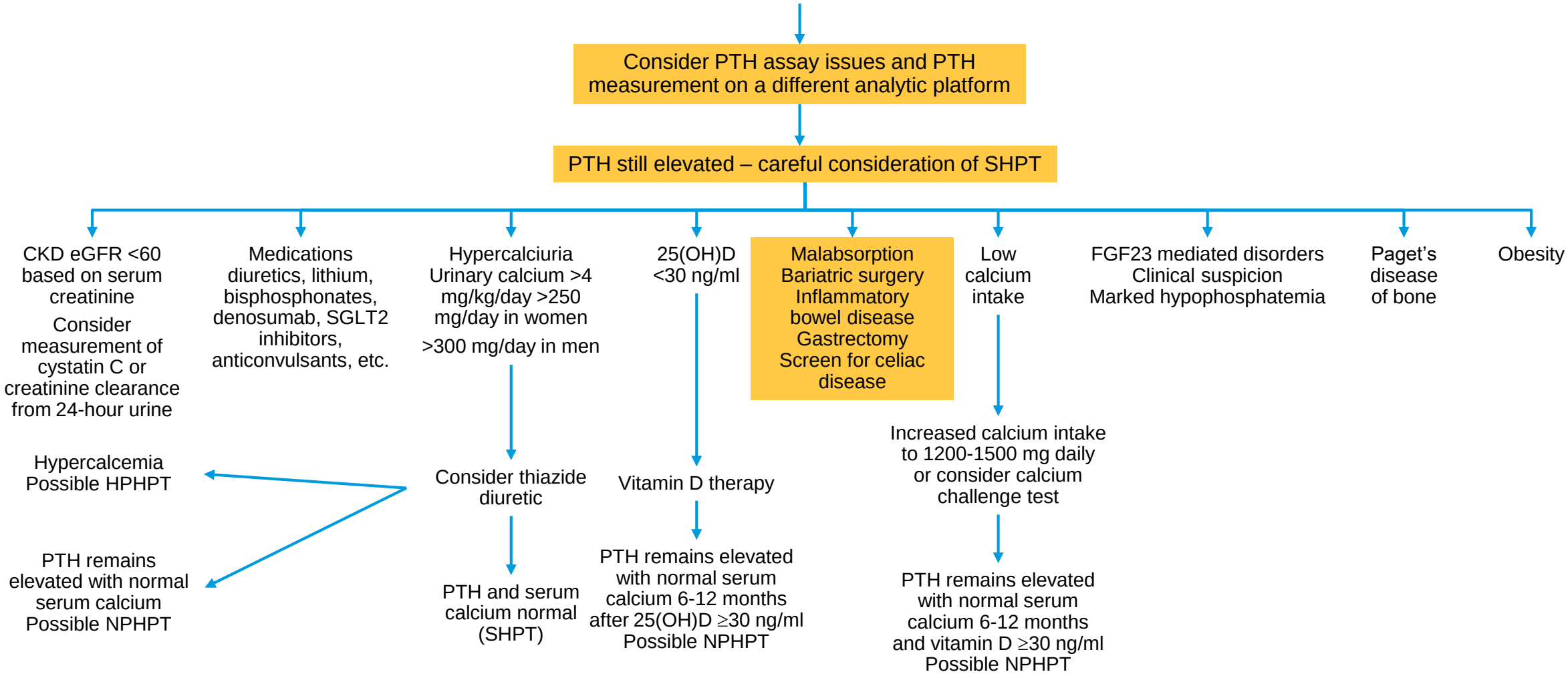
- CBC, ESR, Vitamin B12, Folate, electrolytes, creatinine, SPEP normal
- Serum calcium – 9.0 mg/dL
- Phosphorus – 3.7 mg/dL
- PTH – 90 pg/mL (nl,15-65 pg/mL)
- 25-D – 44 ng/mL
- 24-hour urine calcium < 38 mg with good collection based on 16 mg/kg or urinary creatinine
- TTG Ab > 100 U/mL (nl, < 4 U/mL)
  - Small bowel biopsy c/w malabsorptive pattern

PTH AT 5 YEARS
INTENSIVE THERAPY VS BARIATRIC SURGERY



Crawford MR et al: Endocr Pract 2018;24:256

Approach to the patients with persistently elevated PTH and persistently normal albumin-corrected serum calcium and ionized calcium with no known cause of SHPT



Shaker JL and Wermers RA. J Endocr Soc 2023

WHAT ARE THE KEY TESTS TO EVALUATE EUCALCEMIC HYPERPARATHYROIDISM?

- Repeat PTH on different platform with calcium, phosphorus, and albumin
- Assessment of renal function
  - Creatinine with eGFR or cystatin C
- 24-hour urine calcium, creatinine (sodium as indicated)
- 25-hydroxyvitamin D
- Hypophosphatemia evaluation if applicable
  - FGF 23, TRP, 1,25-$(D)_2$, HCO3, UA

CASE 2

CASE 2

- 59-year-old female diagnosed with osteoporosis 8 years prior based on BMD without fractures
- On oral bisphosphonates since diagnosis and taking correctly
- Takes 500 mg elemental calcium BID and multivitamin
- Gets an estimated 500 mg of dietary calcium
- Walks routinely

CASE 2 (CONTINUED)

- Risk factors
  - Menopause at 50 years of age
  - Chronic PPI therapy
  - Quit smoking 20 years ago
- Current BMD
  - Worst hip T-score -3.1 with 4.3% decline last 2 years
  - Lumbar spine T-score -3.5 with 5.5% increase last 2 years but decreasing trend from baseline

MEDICATIONS

- Aspirin 81 mg daily
- Ibandronate 150 mg once monthly
- Multivitamin daily
- Fish oil 1200 mg twice daily
- Calcium carbonate 500 mg/500 IU BID
- Fluticasone 50 mcg in each nostril twice daily
- Rizatriptan 10 mg as needed
- Simvastatin 20 mg daily
- Doxycycline 40 mg daily
- Loratadine 10 mg daily
- Lansoprazole 30 mg daily

PHYSICAL EXAMINATION

- Weight 68.2 kg; Height 163.8 cm; BMI 25.42; BP 173/94; pulse 80
- Well tanned
- Normal TUG and one-legged stance test
- Rest unremarkable

SECONDARY CAUSE EVALUATION

- Normal tests
  - CBC, 25(OH)D, SPEP, TSH, Celiac screen, chemistry panel including serum creatinine, sodium, liver transaminases, and alkaline phosphatase
  - BAP and Beta CrossLaps in premenopausal range
- PTH 74 pg/mL with calcium 9.1 mg/dL and phosphorus 3.8 mg/dL
- 24-hour urine calcium 412 mg with good collection based on 15.8 mg of urinary creatinine per kg
  - 24-hour urine sodium 84 mmol

WHAT IS YOUR DIAGNOSIS?

A. Normocalcemic PHPT

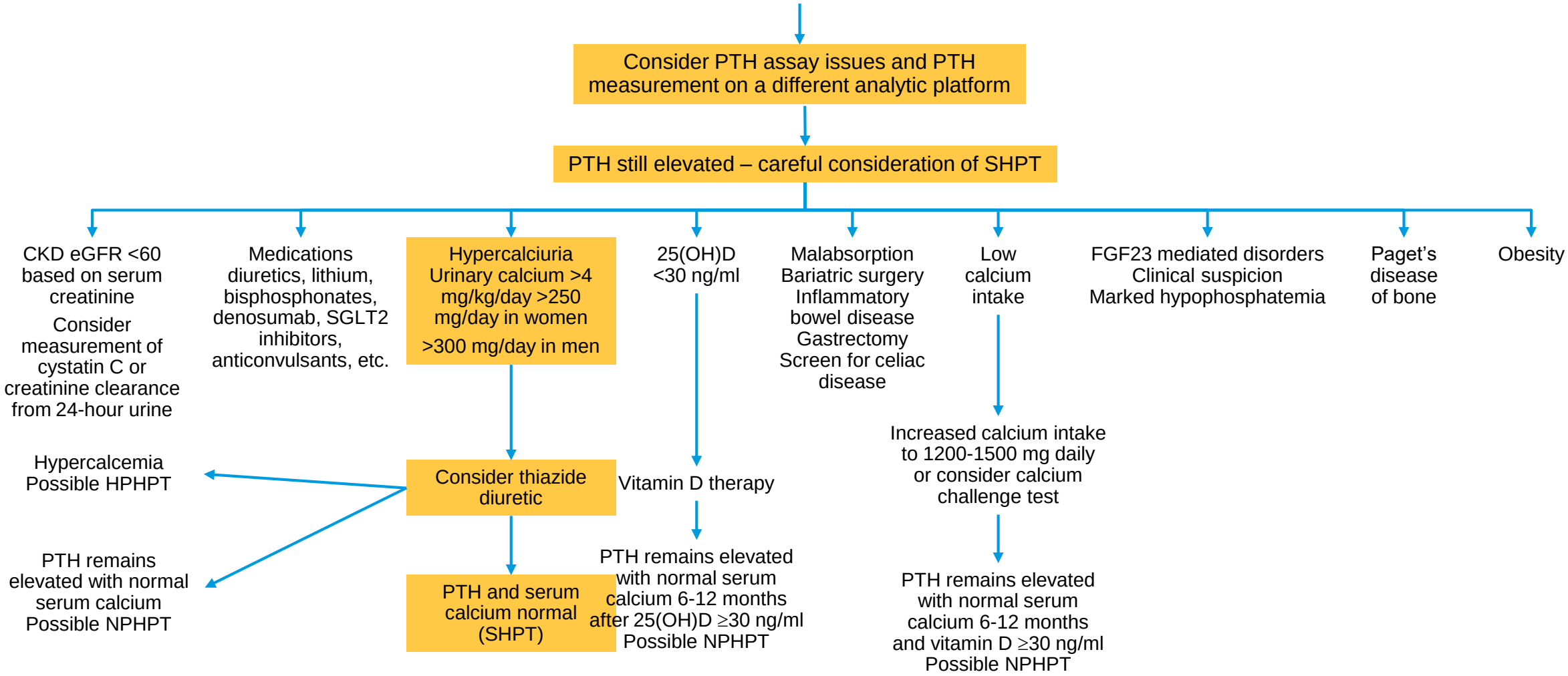
B. Secondary HPT due to ibandronate

C. Inaccurate PTH due to interfering factor

D. Secondary HPT due to hypercalciuria

E. Age appropriate PTH

Approach to the patients with persistently elevated PTH and persistently normal albumin-corrected serum calcium and ionized calcium with no known cause of SHPT



Shaker JL and Wermers RA. J Endocr Soc 2023

PATIENT FOLLOW-UP

- Hydrochlorothiazide 25 mg daily started
- Repeat labs
  - 24-hour urine calcium 174 mg
  - PTH 38 pg/mL
  - Calcium 9.8 mg/dL
  - Phosphorus 4.4 mg/dL
- Last follow-up (10 years after initial visit)
  - PTH 50 pg/mL, calcium 9.9 mg/dL, phosphorus 3.5 mg/dL and 24-hour urine calcium 149 mg

CASE 3

CASE 3

- 49-year-old female referred for evaluation of hyperparathyroidism
- Prior to presentation
  - After fell off a stool, patient had CXR done showing T12 compression fracture (also previous C7 fracture)
  - DXA: showed osteopenia
    - Worst hip T-score -1.5
    - Lumbar spine T-score -1.6

INITIAL LABS

- Serum calcium 9.7 mg/dl, phosphorus 2.9 mg/dl and PTH 90 pg/mL
- 25(OH)D 24 ng/ml
- Alkaline phosphatase 103 U/L
- Serum creatine with eGFR normal
- 24-hour urine calcium 347 mg/spec

CASE 3 (CONTINUED)

- Premenopausal
- No significant GI or renal history including bariatric surgery or kidney stones
- Estimated daily dietary calcium intake 600 mg
- No medications
- Physical examination unremarkable

CASE 3 (CONTINUED)

- Increased dietary calcium intake to goal of 1000 mg daily
- Start hydrochlorothiazide 25 mg daily
- Follow up laboratories
  - Serum calcium 10.5 mg/dL and 10.7 mg/dL
  - PTH high normal
  - 24-hour urine calcium 260 mg

WHAT IS YOUR DIAGNOSIS?

A. Normocalcemic PHPT

B. Secondary HPT due to reduced calcium intake

C. Inaccurate PTH due to interfering factor

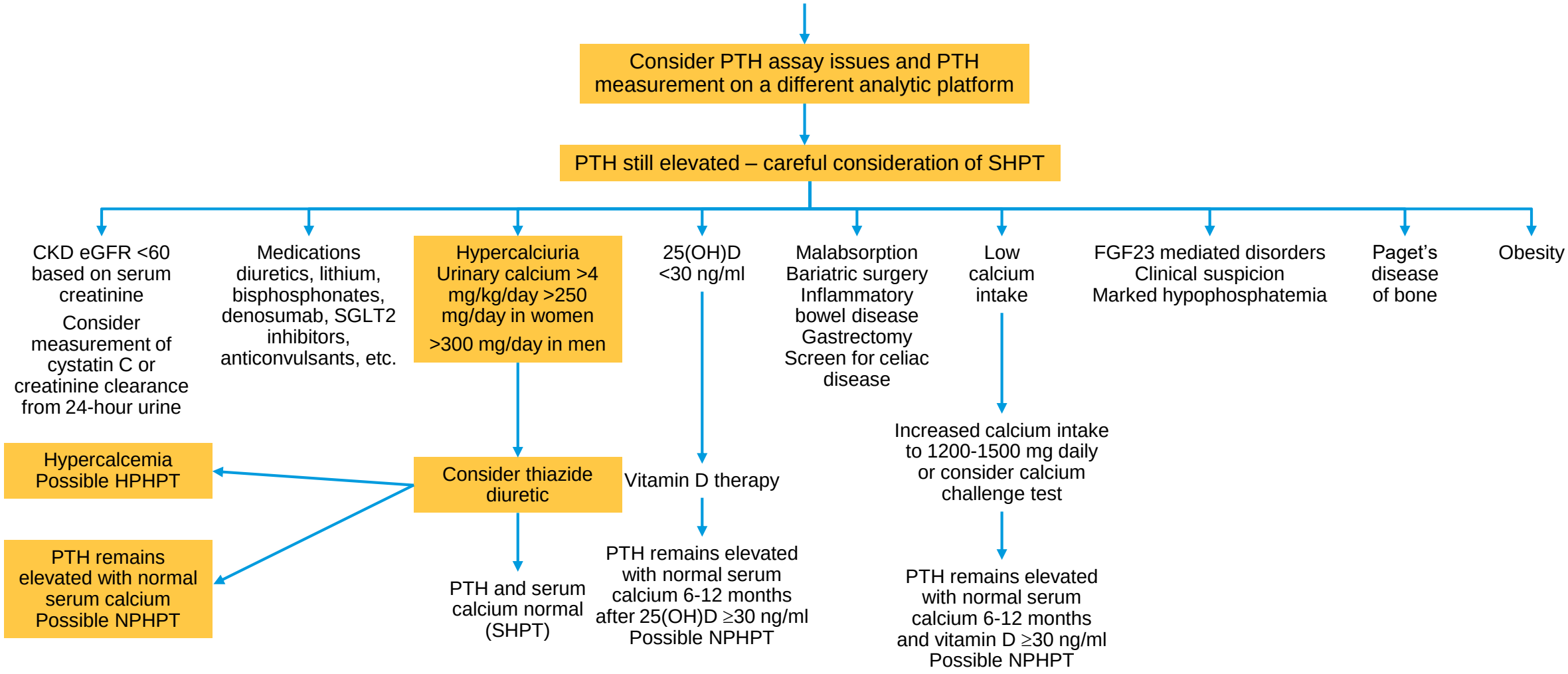
D. Secondary HPT due to hypercalciuria

E. Age appropriate PTH

PATIENT FOLLOW-UP 2 YEARS LATER

- Patient fracture fibula
- BMD demonstrated worsening (still premenopausal)
  - Lumbar spine T-score -2
  - Worst hip T-score -1.7
- Localization with US and sestamibi
  - Concordant for right inferior parathyroid lesion
- Minimal access parathyroidectomy 260 mg parathyroid adenoma with IOPTH ≥ 50% drop

Approach to the patients with persistently elevated PTH and persistently normal albumin-corrected serum calcium and ionized calcium with no known cause of SHPT



Shaker JL and Wermers RA. J Endocr Soc 2023

WHAT CLINICAL FEATURES ARE SUSPICIOUS FOR NORMOCALCEMIC PHPT?

- High normal calcium (vs lower normal) or intermittently elevated
- High incidence rate population
  - Female
  - Older age
- Persistently elevated PTH
- Mildly low phosphorus without elevated alkaline phosphatase
- Normal or elevated 24-hour urine calcium

NORMOCALCEMIC PHPT
CLINICAL FEATURES

- Women (35/37) and postmenopausal (29) with mean calcium 9.4 mg/dL (2.35 mmol/L)
- 7/37 (19%) became hypercalcemic upon yearly evaluation
  - ✓Higher baseline calcium (9.7 mg/dL) (2.43 mmol/L)
  - ✓Older
  - ✓Higher baseline 24-hour urine calcium
- 3/7 (43%) surgery patients – multigland disease

Lowe H et al: J Clin Endocrinol Metab 92:3001, 2007

“MILD PHPT” (25% MCR PHPT REFERRALS)
NORMAL PTH OR NORMOCALCEMIC

- Increasing number of surgical patients with “mild PHPT”
  - 27% from 2001-2012 at referral center
    - 31.4% normocalcemic PHPT and 68.6% with normal PTH
- More likely to have multigland disease (27%)
- More than twice the number of kidneys stones
- Higher likelihood of negative localization (18% vs 5%) persistent PHPT after surgery (12% vs 4%)

Schneider DF et al: Ann Surg Oncol 2013;20:4205-4211
Orr LE et al. World J Surgery 2018;42:409-414

CASE 4

CASE 4

- A 65-year-old female sends you a portal message after her local provider checked a PTH and calcium 8 months after a parathyroidectomy
  - PTH 105 pg/mL and serum calcium 9.5 mg/dL
- Her preoperative PTH was 256 pg/mL with a serum calcium of 10.8 mg/dL, normal 25(OH)D, and 24-hour urine calcium of 190 mg
- She had successful removal of a 240 mg right inferior parathyroid adenoma and IOPTH dropped ≥ 50%
- She is getting 1200 mg of calcium between diet and supplements and is taking 1000 IU of vitamin D3

WHICH OF THE FOLLOW WOULD YOU TELL THE PATIENT?

A. You have normocalcemic PHPT.

B. You have secondary PHPT.

C. You have no evidence of normocalcemic PHPT and you can observe without future concern.

D. You have an elevated PTH after successful parathyroid surgery and may be at increased risk for recurrent PHPT in the future.

E. Follow up with your primary provider. As a trained professional, I can assure you that your PHPT has been cured.

PERSISTENT AND RECURRENT PHPT

DEFINITIONS

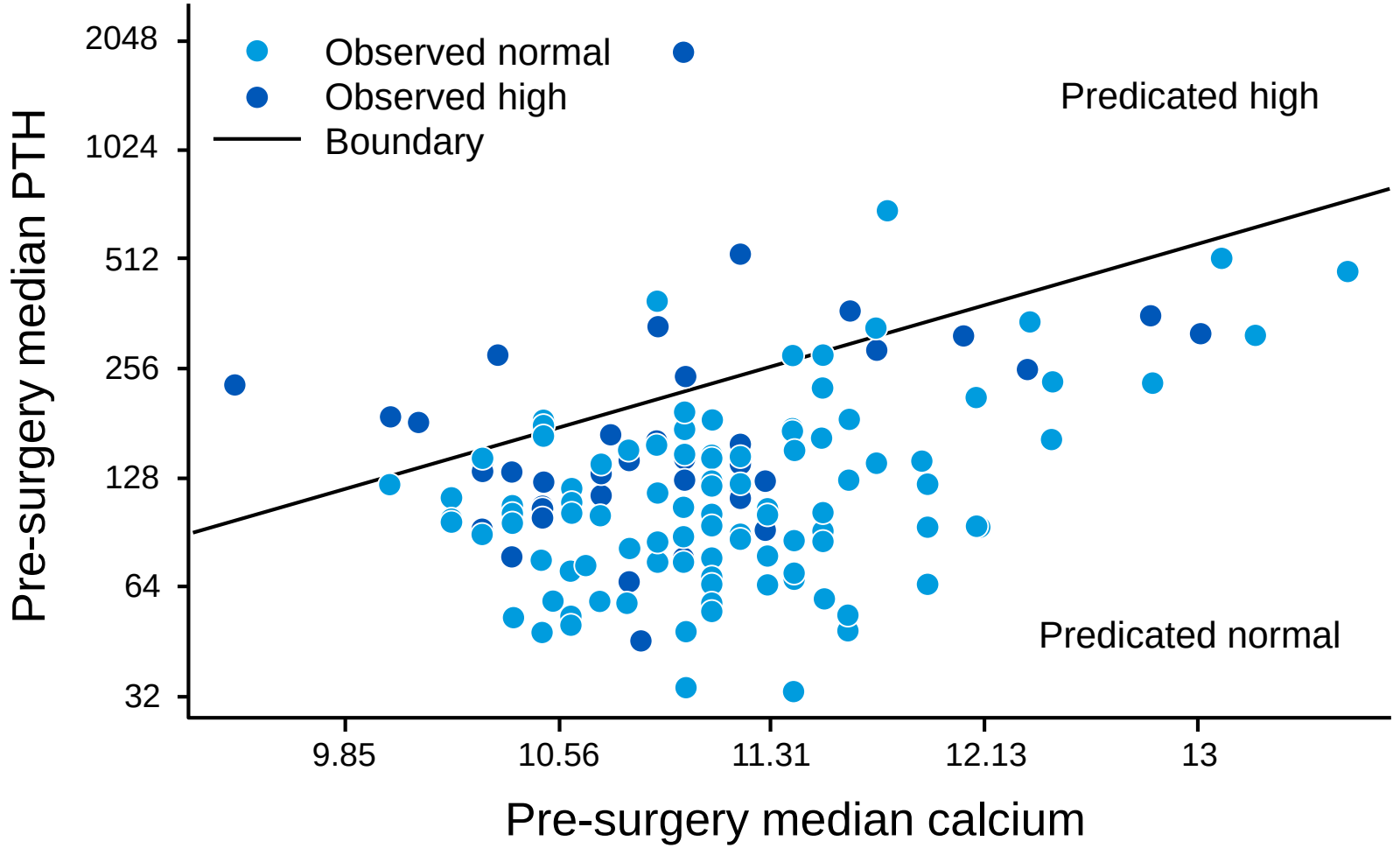
- Persistent PHPT
  - Fail of biochemical cure within 6 months after parathyroid surgery with **hypercalcemia** and inappropriate PTH
- Recurrent PHPT
  - Initial biochemical cure **(normocalcemia)** followed by **hypercalcemia** > 6 months after surgery with inappropriate PTH

PERSISTENTLY ELEVATIONS IN PTH AFTER PARATHYROIDECTOMY

- Retrospective study of 144 patients with lab results within 3-18 months after parathyroid surgery
  - 97% normal serum calcium
  - 30% elevated PTH
    - No significant differences from those with normal PTH regarding age, sex, BMI, gland weight
    - Higher presurgical PTH (156 pg/mL vs 102.5 pg/mL) was significantly associated

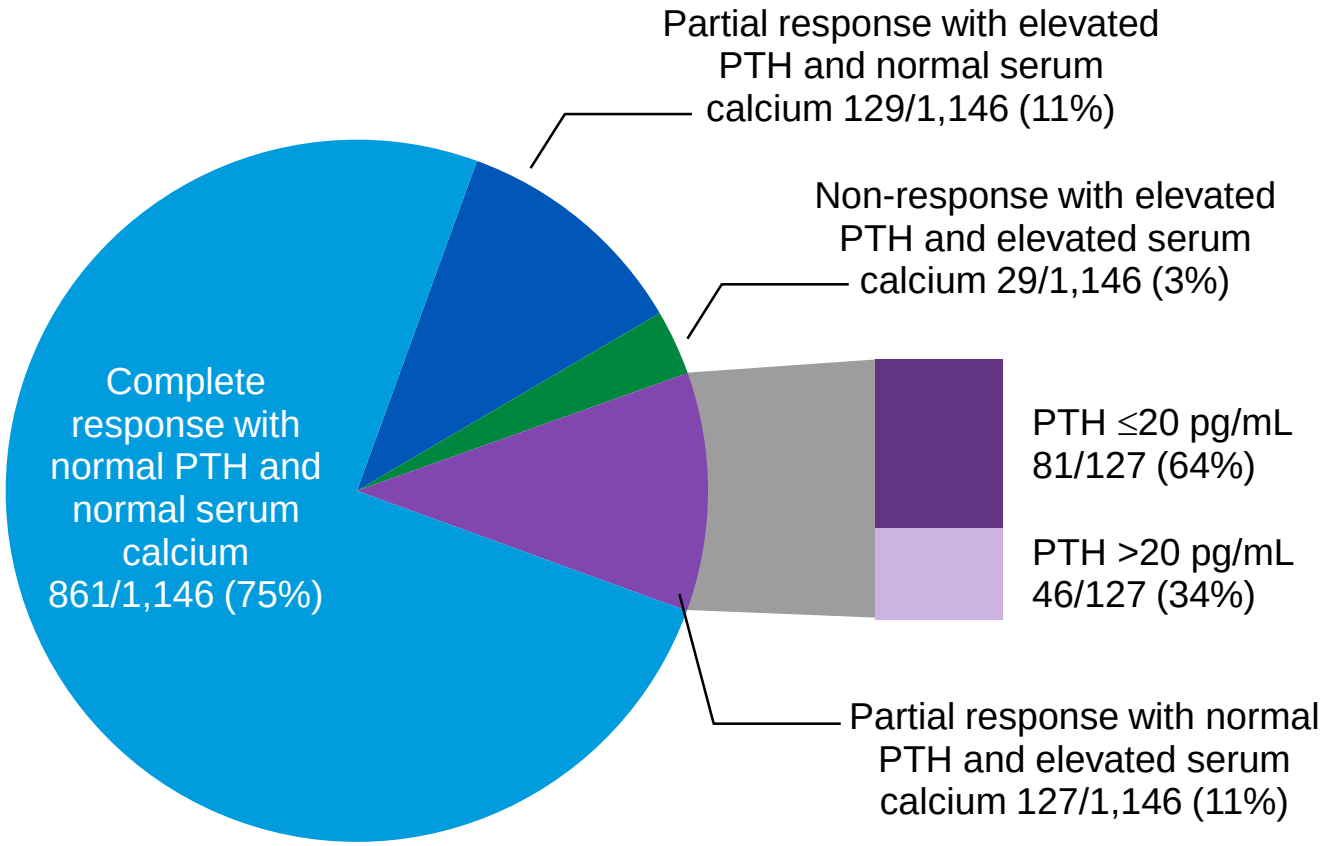
Caldwell M et al. J Clin Endocrinol Metab 2019;104:4473-4480

HIGHER PTH AND LOWER CALCIUM PREOP PREDICTS PERSISTENT PTH ELEVATION POSTOP



Caldwell M et al: J Clin Endocrinol Metab 104:4473, 2019

LABS WITHIN 6 MONTHS AFTER PARATHYROIDECTOMY



Ryder CY et al: Surgery, 2020

EARLY BIOCHEMICAL PREDICTORS OF RECURRENT HYPERCALCEMIA AND PHPT

Early biochemical response	Any episode of recurrent hypercalcemia*	P	Confirmed recurrent HPT†	P
Complete response with normal PTH and normal serum calcium	188 of 861 (22%)	<0.01	57 of 861 (6.6%)	<0.02
Partial response with increased PTH and normal serum calcium	44 of 129 (34%)		35 of 129 (27%)	
Partial response with normal PTH and increased serum calcium	45 of 127 (35%)		20 of 127 (16%)	
Overall	277 of 1,117 (25%)		112 of 1,117 (10%)	

*Recurrent hypercalcemia was defined as any episode of a single serum calcium >10.2 mg/dL at any time during follow-up >180 days after PTX

†Confirmed recurrent PHPT defined as any episode of a serum calcium >10.2 mg/dL and any episode of a PTH >75 pg/mL at any time during follow-up >180 days after PTX. Long-term PTH lab data were available for 724 of 1,117 (65%)

Risk of recurrent PHPT in multivariate analysis

- 2.7 times greater if increased calcium and normal PTH (P<0.02)
- 4.3 times greater if normal calcium and increased PTH (P<0.02)

Ryder CY et al: Surgery, 2020

PERSISTENT AND RECURRENT PHPT OLMSTED COUNTY 1965-2010

- 345 patients with median follow up of 16.7 years
  - 15% recurrence
  - Median time to recurrence of 12.2 years
- Multivariate analysis significant risk factors for recurrence
  - Preop serum calcium > 11 mg/L and PTH < 90 pg/mL
- 51% of patients had at least 1 elevated serum calcium
  - Most (72%) were transient or secondary to other factors (medications, malignancy, etc.)

Szabo YT et al. Ann Surg 2022

Questions & Discussion