Pennsylvania Academy of Family Physicians Foundation

Pittsburgh CME Conference

November 7 - 9, 2014

Hyperparathyroidism ***(Patient Safety)***

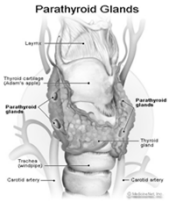
Kelly McCoy, MD
University of Pittsburgh Physicians, Pittsburgh, PA

Disclosures:

Speaker has no disclosures and there are no conflicts of interest.

The speaker has attested that their presentation will be free of all commercial bias toward a specific company and its products.

The speaker indicated that the content of the presentation will not include discussion of unapproved or investigational uses of products or devices.



Pennsylvania Academy of Family Physicians
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Parathyroid Disease: Update on Diagnosis and Management

Kelly McCoy, MD, FACS
Division of Endocrine Surgery
University of Pittsburgh

Disclosure

- Dr. Kelly McCoy has no conflict of interest, financial agreement, or working affiliation with any group or organization.

Learning Objectives

- Discuss the history of parathyroid surgery
- Discuss the diagnosis of primary hyperparathyroidism
- Review surgical indications
- Discuss parathyroid imaging
- Discuss potential pitfalls in parathyroid surgery
- Discuss secondary & tertiary hyperparathyroidism
- Review associations of hyperparathyroidism and MEN

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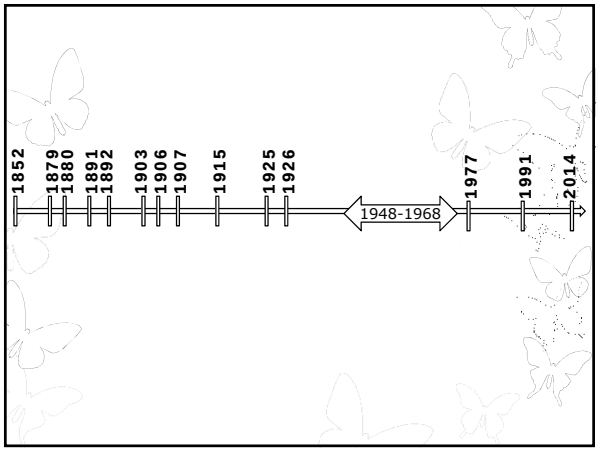

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Primary Hyperparathyroidism

- **Primary Hyperparathyroidism (PHP)**
  - **Affects > 1:1000 people**
  - **Incidence peaks at age 70-80 years**
  - **3:1 female to male distribution**
  - **100,000 new US cases per year**
- **Pathologic Causes of PHP**
  - **Adenoma 85%**
  - **Carcinoma 1%**
  - **Multiglandular Disease 14%**

Risk Factors for PHP

1. Childhood head & neck irradiation
   - 2.5X increased risk for PHP
2. Long-term lithium therapy
   - Prevalence of PHP 15-60%
3. Hereditary syndrome
   - MEN1, MEN2a, HPT-JTS, FHH
4. Chronic vitamin D deficiency?

Clinical Features of PHP

- Osteoporosis
- Nephrolithiasis/nephrocalcinosis
- Peptic ulcer disease, Heartburn, Pancreatitis
- Bone, joint and muscle pain
- Fatigue, Weakness, Depression
- Memory Loss, Polyuria, Sleep Disorder
- Hypertension, Hyperlipidemia, CV disease
- Premature death

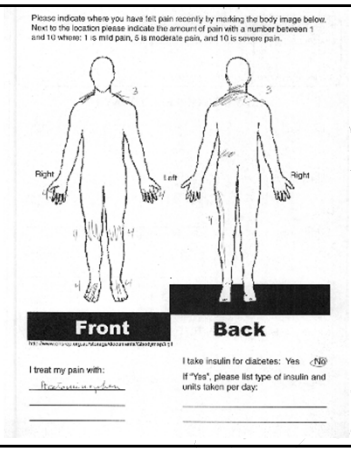
Clinical Features of PHP known to Improve with Curative Surgery

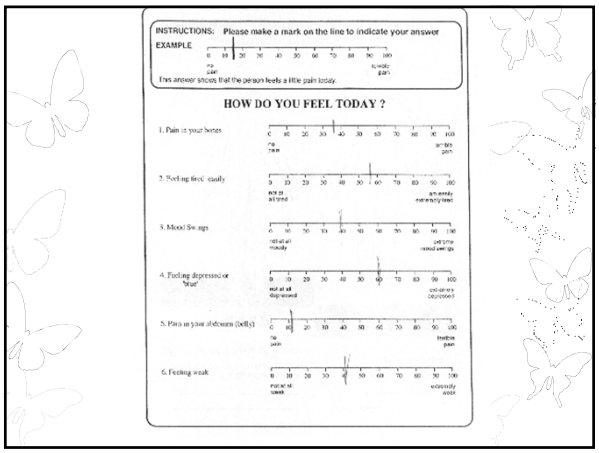
- Osteoporosis
- Nephrolithiasis/nephrocalcinosis
- Peptic ulcer disease, Heartburn, Pancreatitis
- Bone, joint and muscle pain
- Fatigue, Weakness, Depression
- Memory Loss, Polyuria, Sleep Disorder
- Hypertension, Hyperlipidemia, CV Disease
- Premature death

The long-term benefit of parathyroidectomy in primary hyperparathyroidism: A 10-year prospective surgical outcome study

Janice L. Pasieka, MD, Louise Parsons, MSc, *and* Jean Jones, *Calgary, Alberta, Canada*

- Compared PHPT patients with patients undergoing thyroidectomy
- Compared 5 "vague" symptoms: tired, forgetful, irritable, depressed, mood swings
- Compared to Tx patients parathyroidectomy patients had significantly improved QOL at 1 and 10 years





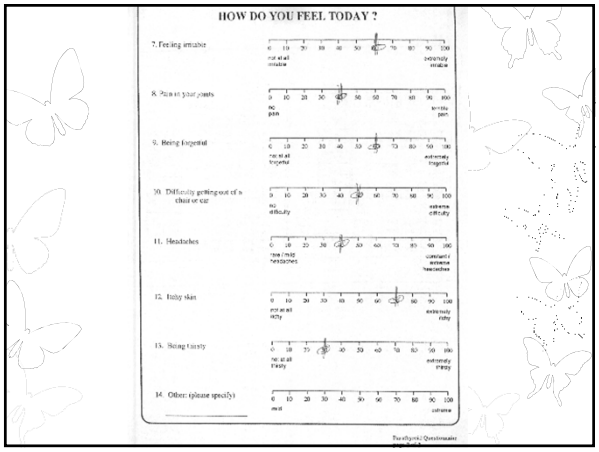
INSTRUCTIONS: Please make a mark on the line to indicate your answer

EXAMPLE

This answer shows that the person feels a little pain today.

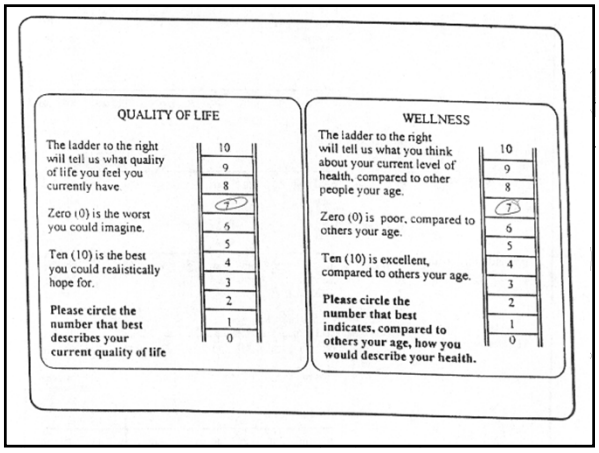
HOW DO YOU FEEL TODAY ?

1. Pain in your bones
2. Feeling tired/ easily
3. Mood Swings
4. Feeling depressed or "blue"
5. Pain in your abdomen (belly)
6. Feeling weak



HOW DO YOU FEEL TODAY ?

7. Feeling irritable
8. Pain in your joints
9. Being forgetful
10. Difficulty getting out of a chair or car
11. Headaches
12. Itchy skin
13. Being Tired
14. Other: (please specify)



QUALITY OF LIFE

The ladder to the right will tell us what quality of life you feel you currently have

Zero (0) is the worst you could imagine.

Ten (10) is the best you could realistically hope for.

Please circle the number that best describes your current quality of life

10 9 8 (7) 6 5 4 3 2 1 0

WELLNESS

The ladder to the right will tell us what you think about your current level of health, compared to other people your age.

Zero (0) is poor, compared to others your age.

Ten (10) is excellent, compared to others your age.

Please circle the number that best indicates, compared to others your age, how you would describe your health.

10 9 8 (7) 6 5 4 3 2 1 0

Benefits of Curative Parathyroidectomy

- Protects renal function
- Improves bone health
- Improves cardiovascular function
- Improves neuropsychiatric health
- Cost efficacy compared to surveillance

Benefits of Curative Parathyroidectomy Relief of Fibromyalgia Symptoms

- 2184 patients from 1995-2013 who had parathyroid exploration for PHP
- 80/2184 (4%) had a concomitant fibromyalgia (FM) diagnosis
- 89% of cured patients had relief of ≥1 symptom
- Improvement in ≥2, ≥3, ≥4 FM symptoms was seen in 71%, 43% and 25% respectively
- QOL and wellness improved in 50%
- 21% of FM patients stopped ALL meds prescribed for FM! Did they really have FM?
- PHP should be excluded before an FM diagnosis is made

Adkisson et al. Surgery. Dec, 2014, in press

Diagnosis of PHP is Biochemical

- Elevated levels of calcium and intact parathyroid hormone
- Normal or increased 24h-urine calcium excretion
- Normal Vitamin D-25 OH

Diagnosis of PHP is Biochemical

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- Imaging has no role in the DIAGNOSIS of hyperparathyroidism

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- Imaging has no role in the DIAGNOSIS of hyperparathyroidism

Familial Hypocalciuric Hypercalcemia (FHH)

- Mutation in the CASR gene
- Inherited in autosomal dominant manner
- Rare
- Red flag is low 24 hour urine
- Repeat labs
- If repeat 24 hour urine Ca below normal levels, genetic testing

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2002 NIH and 2008 AACE Operative Criteria for Asymptomatic PHP

- Hypercalcemia 1.0 mg/dL >upper limit
- Estimated GFR <60 mL/min
- Life-threatening hypercalcemic episode
- Age <50 y
- Dexa bone density T-score <-2.5
- Co-morbidities that complicate surveillance
- Noncompliance to follow-up
- Patient Request

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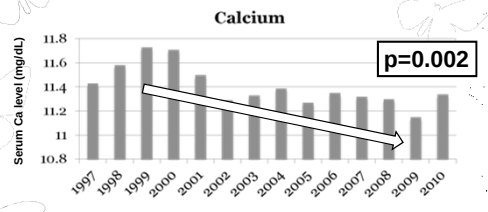
Patients Diagnosed Earlier and with "Asymptomatic" Disease



- Routine biochemical screening for serum calcium levels (started in 1993)
- PHP trends over time: 1011 pts (1997-2011)

McCoy, et al. World J Surg. Jun 2014

Indications for Parathyroid Re-exploration

- Serum calcium level >12 mg/dL
- Nephrolithiasis
- Progression of osteoporosis
- At most centers: positive imaging results

Complications of Parathyroid Surgery

	Initial
Failure	1-3%
Hypopara	1-2%
RLN Paralysis	1%
Hematoma	0.3%
Costs	Effective

Complications of Parathyroid Surgery

	Initial	Reoperative
Failure	1-3%	5-10%
Hypopara	1-2%	5-10%
RLN Paralysis	1%	5%
Hematoma	0.3%	0.3%
Costs	Effective	Much Higher

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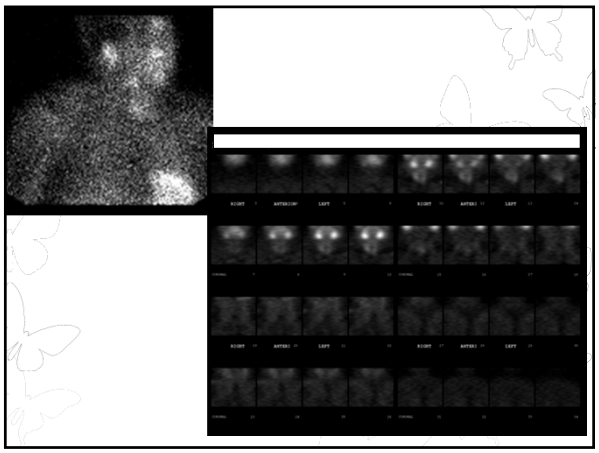
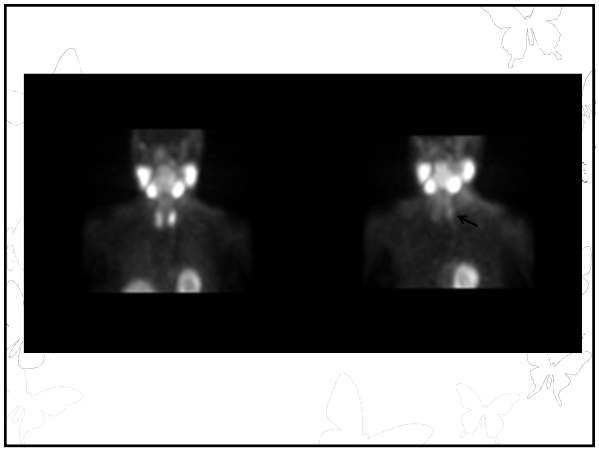
Imaging

- Ultrasound
  - Seeks enlarged glands
  - Evaluates for concomitant thyroid disease
- Sestamibi
  - Planar
  - SPECT
  - SPECT + CT
- 4D CT, MRI






Spin: 0
Tilt: -90
F

Sestamibi SPECT Intensity Scoring System in Sporadic Primary HPT Yip L, WJS 2009.

- Scored SPECT results correlated stepwise with anatomic rates of MGD
- A negative scan = 22% MGD with 7% operative failure rate (overall failure 2.8%)
- Only 26% of scans that were read as MGD, actually had MGD at exploration
- Conclusion: Expert surgeons must use validated adjuncts to exclude MGD

Successful Parathyroidectomy

- Success = durable normalization of calcium levels at 6 months
- Operative failure = morbid and costly
- Adenomectomy is fun, but surgery for cure obligates the use of a validated technique to exclude Multiglandular Disease

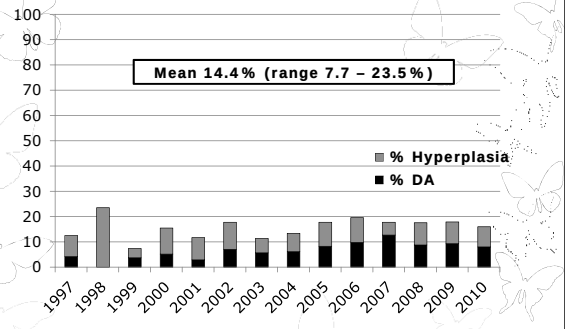
Techniques to exclude MGD

- Proven:
  - Bilateral Four-gland Exploration
  - Intraoperative PTH Monitoring
- Disproven or Unproven:
  - All Imaging techniques including Sestamibi, US, and probe radio guidance
  - Unilateral "adenomectomy" without IOPTH

MGD - suspicion

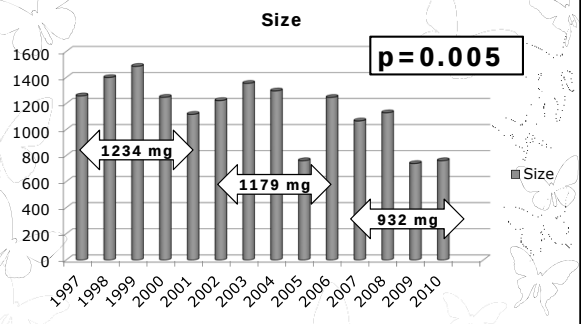
- Negative or equivocal imaging
- Gland size
- IOPTH
- PMH, Family history

Multiglandular Disease By Year



McCoy, et al. World J Surg. Jun 2014

Size over time



McCoy, et al. World J Surg. Jun 2014

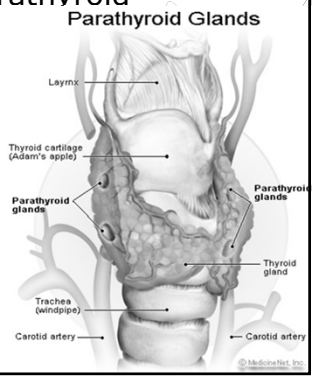
Gland size and MGD

- When the 1st resected gland was <200 mg, MGD rate higher
  - >200 mg – 11.3%
  - **<200 mg – 39.7%**

p=0.001

Two Pearls of Parathyroid Exploration

- The best localization technique is an experienced parathyroid surgeon
- Imaging tells you where to start looking and QPTH tells when you can stop looking
- Bottom line – Surgeons judgment and experience trumps all



Intraoperative PTH

- Allows a focused approach
- Different criteria exist to classify an operation as successful or complete
- We use > 50% drop AND drop into normal range
- IOPTH is ONE of our tools

Intraoperative PTH – how low should it go?

- 1108 patients
- Consecutive initial management for sporadic primary hyperparathyroidism
- All used IOPTH monitoring
- Mean follow-up 1.8 years

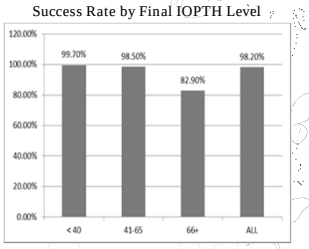
Wharry et al. World J Surg. Mar 2014

Success: eucalcemia at >6 months and throughout observation period

- Success was equally likely with a final IOPTH drop to 41-65 pg/mL versus ≤40 pg/mL

(99.7% vs 98.5%, p=1)

Success Rate by Final IOPTH Level

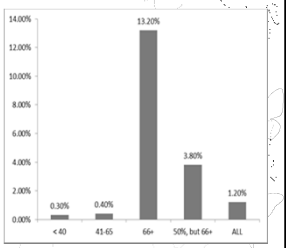


Wharry et al. World J Surg. Mar 2014

Failure: re-demonstration of disease <6 months post op

- 43 times more likely when final IOPTH level did not drop to into the normal range ≤65 pg/mL (13% vs 0.3%, p<0.001)
- 19 times more likely when the final IOPTH level dropped by >50% but not into the normal range (3.8% vs 0.2%, p=0.015)

Failure Rate by Final IOPTH Level



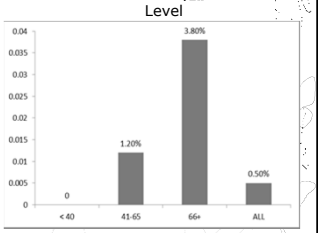
Wharry et al. World J Surg. Mar 2014

Recurrence:- re-demonstration of disease after 6 months post op cure

- More likely with a final IOPTH level of 41-65 pg/mL than with a final IOPTH ≤40 pg/mL

  (3.8% vs 1.2%, p=0.016).
- Occurred at mean 3.2 years

Recurrence Rate by Final IOPTH Level



Wharry et al. World J Surg. Mar 2014

Conclusions

- In unselected patients presenting for management, intraoperative PTH monitoring is a useful adjunct facilitating a very high cure rate (98.2%) for initial surgical management of sporadic primary hyperparathyroidism.
- Together, a final IOPTH level within the normal range **PLUS** a drop by >50% strongly predict operative success (p<.001).
- **Patients with a final IOPTH level between 41-65 pg/mL should be followed beyond 6 months for possible long-term recurrence.**

Who should operate?

- Endocrinesurgery.org
- "In general a surgeon should do more than 50 parathyroid operations a year to be considered an expert"

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PROFILE OF A CLINICAL PRACTICE

Thresholds for Surgery and Surgical Outcomes for Patients with Primary Hyperparathyroidism: A National Survey of Endocrine Surgeons

JULIE ANN SOSA, NEIL R. POWE, MICHAEL A. LEVINE, ROBERT UDELSMAN, AND MARTHA A. ZEIGER

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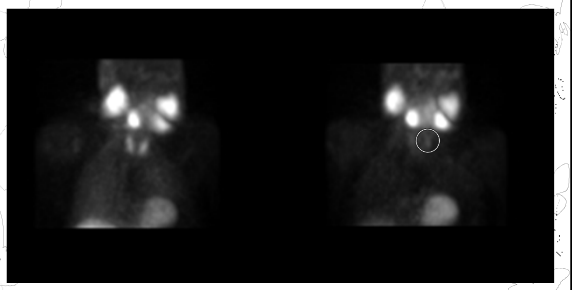
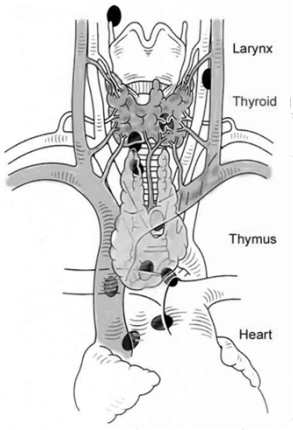
Pearls & Pitfalls

- Trust your instincts more than your tools
- The best imaging can be misleading
- IOPTH rarely is misleading but can be
- Supernumerary glands
- Ectopic glands
- Missed adenoma
- Missed MGD



Pitfalls



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Secondary Hyperparathyroidism

- Most commonly due to ESRD
- Caused by hyperplastic glands
- Can be medically managed with Sensipar
- Surgical intervention may be necessary
- Approach is subtotal parathyroidectomy with cryopreservation

Secondary Hyperparathyroidism

- Indications for surgery
  - Calciphylaxis
  - Intractable pruritis or pain
  - PTH >1000
  - Inability to tolerate Sensipar

Tertiary Hyperparathyroidism

- Long term secondary hyperparathyroidism can lead to autonomous function
- Seen after kidney transplantation in ESRD
- Can be single or multigland disease
- Same biochemical profile & surgical indications as primary hyperparathyroidism

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MEN Syndromes:

- Includes **MEN1 and 2**, Carney Complex, VHL, and NF1
- Similarities: Autosomal Dominant and High Penetrance

	MEN1	MEN2a	MEN2b
Major Manifestations	PHP, Pituitary Adenoma, Pancreatic Neuroendocrine Tumors	MTC, Pheo, PHP	MTC, Pheo, Mucosal Neuromas
Minor Manifestations	Carcinoids, Adrenal Adenomas, Lipomas, Collagenomas, Facial Angiofibromas,	Cutaneous Lichen Amyloidosis, Hirschsprung's	Marfanoid Habitus
Gene	*MEN1*	*RET*	*RET*

Brandi ML, et al. JCEM, 2001.

The '6 Questions' can also diagnose MEN1

- Do you have any blood relatives with:
  1. Neck surgery?
  2. Kidney stones?
  3. Brain tumors?
  4. Ulcers?
  5. High calcium levels?
  6. Pancreatic tumors

- Answering yes to any one, **7x** increased risk of MEN1
- Younger age was also a risk factor

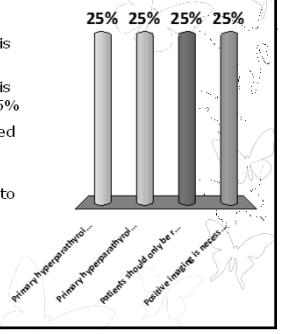
Yip L, et al. Surgery, 2008

Who Should Get Gene Testing?

- Index Case
  - 2/3 major manifestations
  - 1/3 major manifestation with at least one 1st degree relative with 1/3 tumors ("6 Questions")
- Atypical: ≥2 MEN1-related tumors, multiple parathyroid tumors before 30 y, recurrent PHP, history of gastrinoma or multiple islet cell tumors

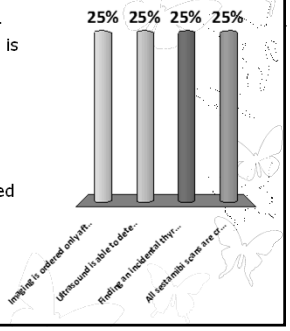
Q #1: Which of the following is true of primary hyperparathyroidism?

A. Primary hyperparathyroidism is more common in men
B. Primary hyperparathyroidism is due to a single adenoma in 85%
C. Patients should only be referred for surgery if they meet NIH criteria
D. Positive imaging is necessary to recommend surgery



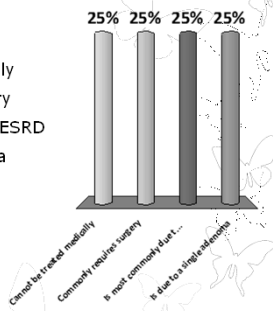
Q #2: Which is true of parathyroid imaging?

A. Imaging is ordered only after primary hyperparathyroidism is confirmed
B. Ultrasound is able to detect ectopic mediastinal glands
C. Finding an incidental thyroid nodule on US is rare
D. All sestamibi scans are created equal



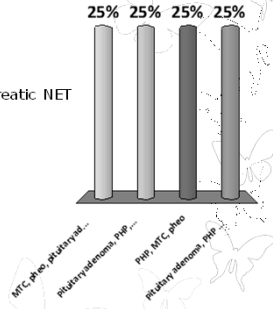
Q #3: Secondary hyperparathyroidism

A. Cannot be treated medically
B. Commonly requires surgery
C. Is most commonly due to ESRD
D. Is due to a single adenoma



Q #4:Which of the following includes the 3 major manifestations of MEN1?

A. MTC, pheo, pituitary adenoma
B. Pituitary adenoma, PHP, pancreatic NET
C. PHP, MTC, pheo
D. Pituitary adenoma, PHP pheo



Questions?