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PEARLS OF LABORATORY MEDICINE

Hypercalcemia: Causes and Laboratory Investigation

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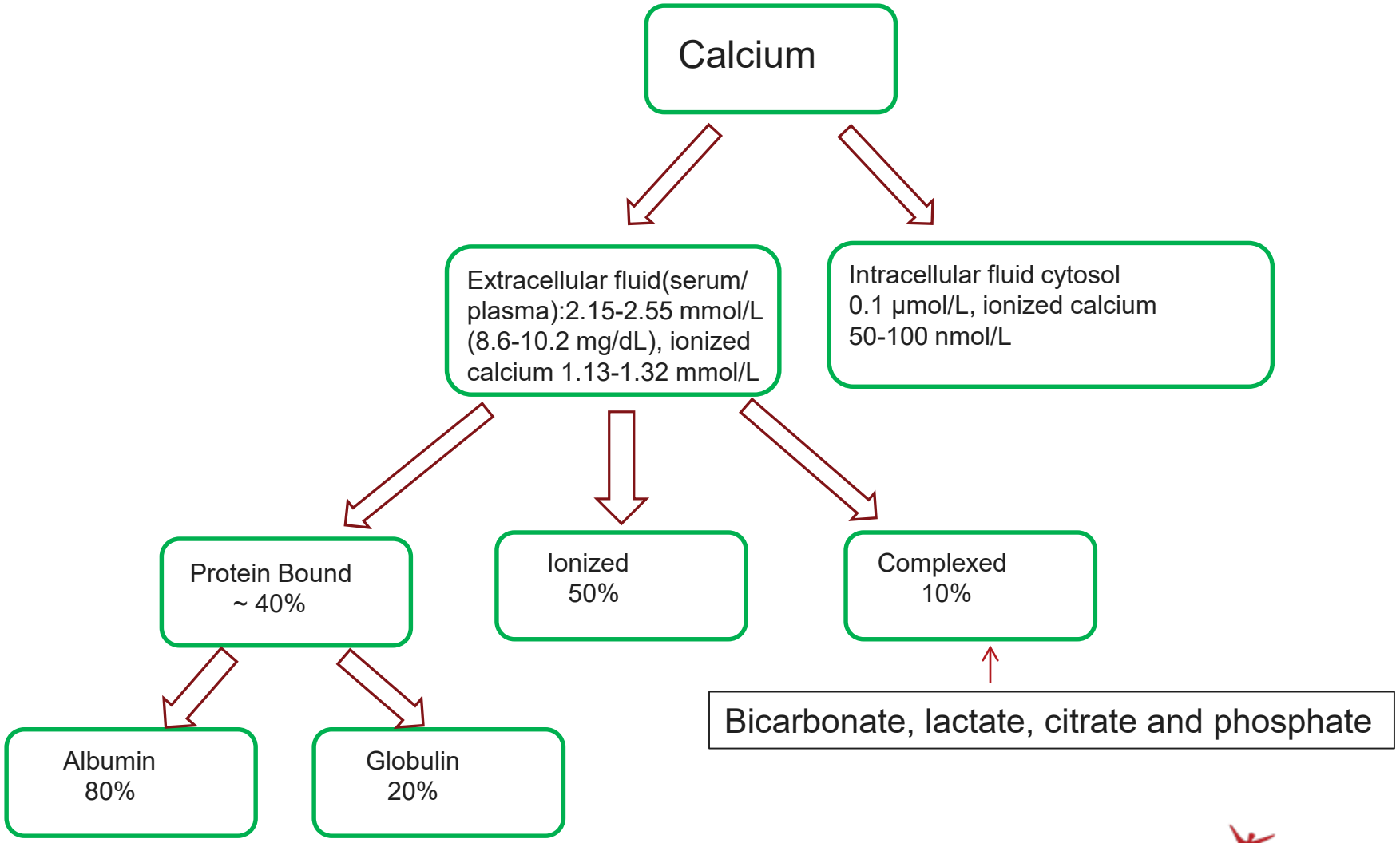
Outline

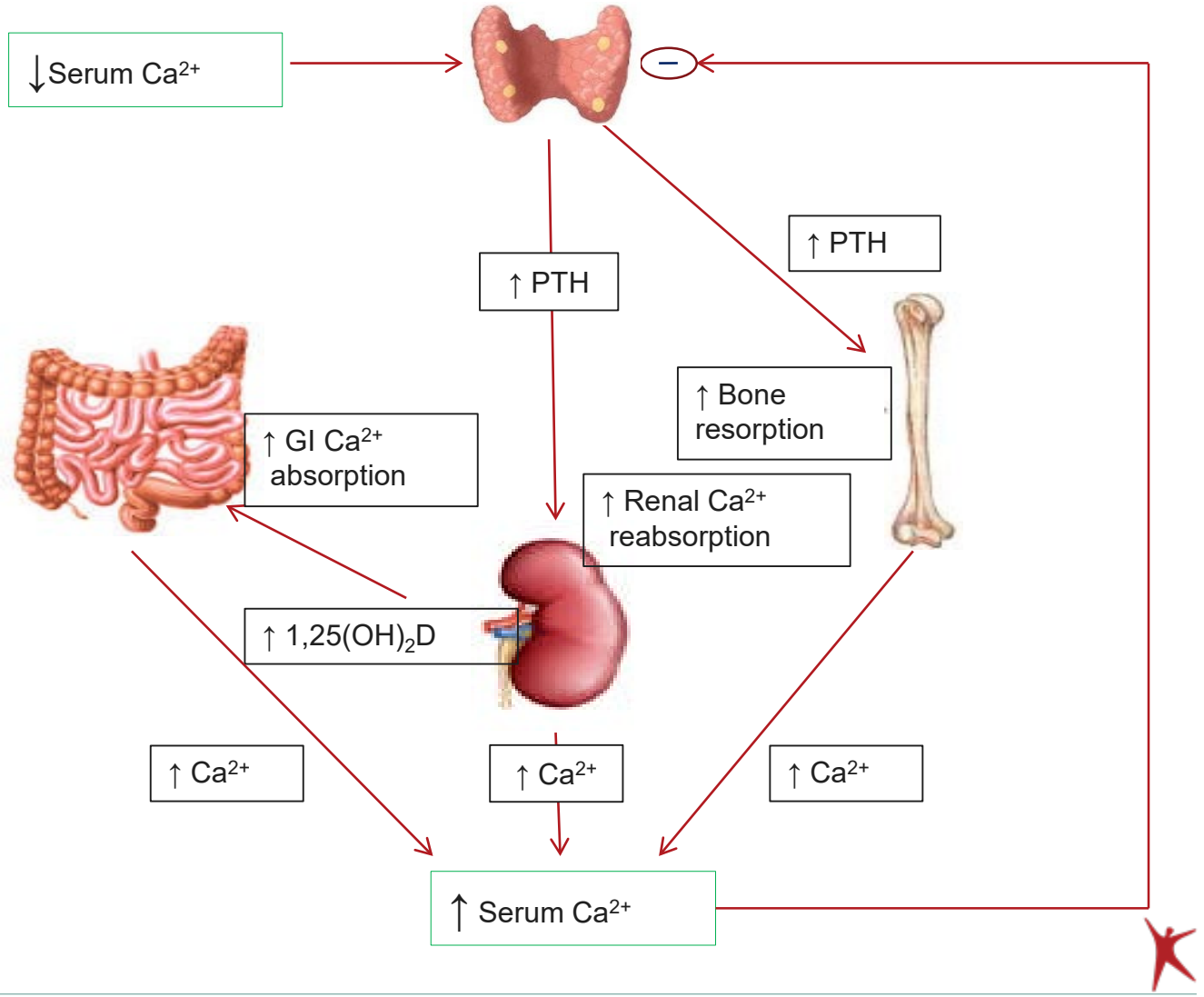
- ❑ Provide brief review on calcium homeostasis
- ❑ Discuss causes of hypercalcemia
- ❑ Identify laboratory approach to hypercalcemia

Distribution of Calcium



Meng QH and Wagar EA. Crit Rev Clin Lab Sci 2015;52:107-19.

Calcium Homeostasis



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Regulation of Calcium Homeostasis

Hormones	Effect on bones	Effect on intestine	Effect on kidneys	Blood level
PTH	↑Bone resorption	↑1,25$(OH)_2$D Indirectly ↑Ca^{2+}, ↑PO_4 absorption	↑Ca^{2+} reabsorption ↓PO_4 reabsorption	↑Ca^{2+} ↓PO_4
1,25 $(OH)_2$ D	Weak effect on bone resorption	↑Ca^{2+}, ↑PO_4 absorption	Weak effect on ↑Ca^{2+} reabsorption	↑Ca^{2+} , ↑ PO_4
Calcitonin	↓Bone resorption	No direct effects	↓Ca^{2+}, ↓PO_4 reabsorption	↓Ca^{2+}, ↓ PO_4

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Causes of Hypercalcemia (1)

Preanalytical errors:

Tourniquet use and venous occlusion: associated with increased-protein bound calcium: total calcium but not ionized calcium
Fist clenching or forearm exercise: decrease in pH and increase in ionized and total calcium
Hyperventilation: Respiratory alkalosis
Changes in posture: standing decreases intra-vascular water and increases protein and thus total calcium
Prolonged immobilization and bed rest: increase both total and ionized

Contamination with calcium: Corks, glassware, tubes, drywall

Analytical interference: Spectrophotometry (HIL) or ISE

Causes of Hypercalcemia (2)

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Clinical Causes of Hypercalcemia:

Parathyroid hormone

Primary hyperparathyroidism

Sporadic, familial, multiple endocrine neoplasia 1 (MEN 1) or MEN 2A

Secondary and Tertiary hyperparathyroidism

Coexisting malignancy and primary hyperparathyroidism

Ectopic PTH in malignancy (very rare)

Malignancy

Humoral hypercalcemia of malignancy

Parathyroid hormone-related protein (PTHrP)

Local osteolysis (mediated by cytokines) multiple myeloma,

Breast cancer, lung cancer - Modulated by Cytokines, chemokines, PTHrP

Vitamin D

Granulomatous disease: sarcoidosis, tuberculosis, berylliosis, coccidioidomycosis: 1,25[OH]2D

Vitamin D intoxication

Vitamin D supplements, vitamin D metabolites or analogs

Lymphoma (1,25[OH]2D)

Causes of Hypercalcemia (3)

Renal Failure

Chronic renal failure with treatment with calcium and 1,25[OH]2D or VitD analogs

Recovery phase of Rhabdomyolysis and acute renal failure

Renal transplant

Other Endocrine

Hyperthyroidism (Thyrotoxicosis)

Adrenal insufficiency

Acromegaly

Pheochromocytoma

Medications:

Thiazide diuretics

Lithium-related release of PTH

Milk–alkali syndrome (calcium and antacids)

Vitamin A intoxication

Theophyline

Other

Immobilization with high bone turnover (e.g., Paget's disease, bedridden patients)

Familial hypocalciuric hypercalcemia

Williams Syndrome

Hyperphosphatemia

Acute hypomagnesemia

In Reality…

- Primary hyperparathyroidism and cancer account for 90% of cases of hypercalcemia
- Outpatients
  - 90% have primary hyperparathyroidism
- Inpatients
  - 65% have cancer
  - 25% have primary hyperparathyroidism

Primary Hyperparathyroidism

- Increased calcium levels due to excessive PTH secretion from parathyroid adenoma (90%) or hyperplasia multiple gland enlargement (10%)
    - MEN 1
    - MEN 2A
    - Familial hyperparathyroidism
    - Carcinoma (<1%)
    - Familial benign hypercalcemia (FBH)
- Hypercalcemia results from combined effects of PTH-induced bone resorption, intestinal calcium absorption and renal tubular reabsorption
- Pathophysiology related to both PTH excess and concomitant excessive production of 1,25-(OH)2-D.

Lab Tests in Diagnosis of Primary Hyperparathyroidism

- Intact PTH and chemistry panel
  - PTH elevated despite elevated serum calcium
  - Serum phosphate in the low-normal to mildly decreased range
  - Serum ALP increased, Hyperchloremic metabolic acidosis
- Urine calcium normal to slightly increase
- 24-hour urine calcium excretion
  - Used to rule out familial hypocalciuric hypercalcemia
  - Values below 100 mg/24 hours or a calcium creatinine clearance ratio of < 0.01 are suggestive of FHH
- Ionized calcium versus serum calcium: an age-old debate...
  -Corrected serum calcium

    Serum calcium (mg/dL)+0.8 [4-albumin (g/dL)]

Mechanisms for Hypercalcemia of Malignancy

Underlying cause is generally excessive bone resorption by one of three mechanisms.

- Humoral hypercalcemia of malignancy: over-expression of PTH-related protein (PTHrP). PTHrP affects bone and kidney
  - Squamous cell carcinoma: lung, head and neck, esophagus, cervix, etc.
  - Carcinoma: ovarian, breast, renal, etc.
- 1,25-(OH)2-D synthesis by lymphomas
- Local osteolytic hypercalcemia (cytokine-mediated) multiple myeloma
  - 20% of all hypercalcemia of malignancy

Laboratory Investigation of Hypercalcemia

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Serum total calcium:
Ionized calcium: more accurate assessment of calcium status
Albumin: useful for corrected calcium
PTH:
25 (OH)vitamin D and 1,25 (OH)2D:
Acid-base status
Electrolytes, Magnesium, Bicarbonate
Serum BUN and creatinine
Serum phosphate
Serum (urine) protein electrophoresis
Urinary calcium (24 hour), calcium to creatinine ratio
Urine creatinine
Urinary cyclic adenosine monophosphate (cAMP):
    cAMP increased in primary hyperparathyroidism
PTHrP:

Laboratory Testing

Initial laboratory testing

- Total Calcium

  Correct value if albumin decreased:

  - Corrected Ca = Ca (mg/dl) + 0.8 (4-albumin [g/dl])

- If calcium elevated above 11.0 mg/dL – order intact PTH
- Ionized calcium
- Electrolytes– including BUN and creatinine
- Phosphorus

Laboratory Testing

- **PTH (intact)**

  Elevated or normal – suggests hyperparathyroidism (elevated calcium should suppress PTH); order urine calcium (24-hour)

  High – primary hyperparathyroidism

  Low (<50-100 mg) – familial hypocalciuric hypercalcemia(FHH)

  Low – order PTHrP or consider other testing for vitamin D excess, milk-alkali syndrome, hyperthyroidism

- **PTHrP**

  Low or normal – order **vitamin D**: 25-(OH)D and 1,25-(OH)2D

  High – lymphoma or granulomatous disease (sarcoidosis, Wegener granulomatosis, Tuberculosis)

  Low – consider testing for cancer

  High – cancer

Additional Investigations:

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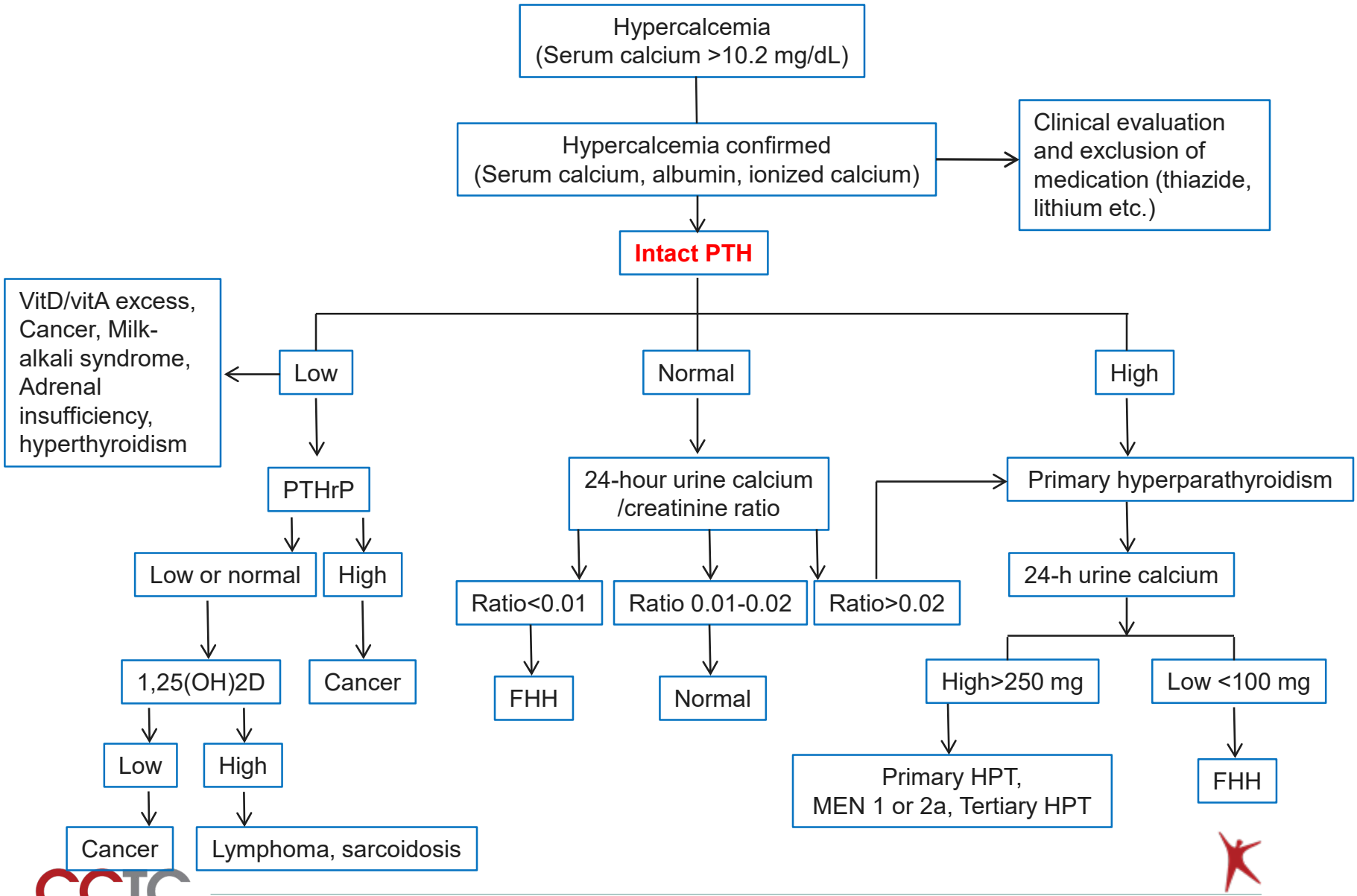
- Chest X-ray: lung cancer or metastases, sarcoidosis, or tuberculosis
- Renal function: renal failure, milk-alkali syndrome, or renal impairment in primary hyperparathyroidism or myeloma
- Complete blood count: hematological malignancy or anemia
- Erythrocyte sedimentation rate or CRP: may be increased in cancer
- Serum alkaline phosphatase: may be increased in primary hyperparathyroidism, Paget's disease with immobilization, myeloma, or bone metastases
- Liver function tests: for liver metastases; chronic liver failure is also a rare cause of hypercalcemia.
- Thyroid function tests: Thyrotoxicosis
- Serum cortisol: Addison's disease is a rare cause.

Investigation of Hypercalcemia



*HPT, hyperparathyroidism; FHH, familiar hypocalciuric hypercalcemia; MEN, multiple endocrine neoplasia

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Summary

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- Primary hyperparathyroidism and cancer are the most common causes of hypercalcemia
- Intact PTH is the most important test in the differential diagnosis of hypercalcemia
- 24 hour urine calcium and calcium to creatinine ratio are helpful
- PTHrP should be measured if cancer is suspected
- Tests for other causes of hypercalcemia should be ordered for differential diagnosis
- An investigation algorithm should be established in each institution

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Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership**:
- **Consultant or Advisory Role:**
- **Stock Ownership:**
- **Honoraria:**
- **Research Funding:**
- **Expert Testimony:**
- **Patents:**

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