PEARLS OF LABORATORY MEDICINE

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TITLE: Hypoparathyroidism

PRESENTER: Ashton Brock, Ph.D.

Slide 1:

Hello, my name is Ashton Brock. I am a clinical chemistry fellow at the University of Virginia. Welcome to this Pearl of Laboratory Medicine on "Hypoparathyroidism."

Slide 2:

Parathyroid hormone, or PTH, is an 84-amino acid peptide hormone that is secreted from the parathyroid gland with the primary function of calcium regulation. For PTH secretion, calcium sensing receptors on the parathyroid gland surface sense ionized calcium concentrations in the blood. In response to low calcium detected by the calcium sensing receptors, the parathyroid secretes PTH to raise extracellular calcium levels. PTH binds PTH receptors on renal tubular cells in the kidney and osteoclasts in the bone, which leads to the stimulation of adenyl cyclase and subsequent increase in cyclic AMP. Cyclic AMP activates phospholipase C, which catalyzes a series of events leading to the release of extracellular calcium. PTH secretion is downregulated with negative feedback from increased calcium concentrations.

Slide 3:

Once secreted, PTH has several actions in respect to calcium and phosphate homeostasis. Phosphate, among other organic acids and proteins, binds calcium ions and lowers the amount of free calcium available for important physiological actions. Therefore, high plasma phosphate concentrations typically lead to hypocalcemia in patients. Thus, when patients have low calcium concentrations and subsequent activation of the parathyroid gland, the secreted PTH has several mechanisms to simultaneously decrease the amount of phosphate while increasing calcium concentrations. In the kidney, PTH stimulates the tubular cells to increase calcium

reabsorption while reducing the expression of the sodium-dependent phosphate cotransporter, leading to enhanced urinary phosphate wasting. Also in the kidney, PTH activates 1α-hydroxylase, which stimulates the conversion of inactive 25(OH) vitamin D to active $1,25(OH)_2$ vitamin D. In the GI tract, this increase in active vitamin D leads to the synthesis of an epithelial calcium ion channel and a cytosolic calcium binding protein, both of which are essential for calcium absorption in the intestine. The absorption of phosphate in the GI tract is also promoted by active vitamin D, but in a less regulated process. In the bone, PTH stimulates the resorption of calcium and phosphate by activating and increasing the number of osteoclasts. Overall, PTH stimulation increases calcium concentrations and decreases phosphate via urinary excretion.

Slide 4:

Because of its significant role in calcium homeostasis, abnormally low or high PTH concentrations can have major physiological effects on the body. Hypoparathyroidism is a condition in which the body secretes low PTH concentrations or has deficient PTH action. In hypoparathyroidism, the concentration of PTH is inappropriately low for patients with hypocalcemia.

Slide 5:

The signs and symptoms of hypoparathyroidism often reflect the signs and symptoms of hypocalcemia. Because of its involvement in muscle contraction and nerve conduction, patients with low calcium concentrations can experience parasthesia, muscle cramps, muscle weakness, twitching, and tetany in the hands and feet. They may also have CNS abnormalities such as depression, altered mental status, seizures, or coma, and cardiac abnormalities such as arrhythmias, hypotension, and heart failure. Respiratory failure from spasms of the airways and bronchi are also associated with hypocalcemia.

Slide 6:

The causes of hypoparathyroidism can be split into 4 categories that often overlap: parathyroid destruction, genetic disorders of PTH synthesis and action, PTH resistance, or reversible impairment of PTH secretion.

Slide 7:

The most common cause of hypoparathyroidism is parathyroid destruction. It can occur in several ways. First, destruction can occur through iatrogenic causes such as a parathyroidectomy or irradiation. Less common causes of parathyroid destruction are autoimmune illnesses such as autoimmune hypoparathyroidism and type 1 autoimmune

polyglandular syndrome (also known as type 1 APS), which severely damages the parathyroid tissue and impairs the PTH-secreting cells. Another cause of parathyroid destruction is due to infiltration of the parathyroid glands by an infiltrative process, such as Wilson's disease, iron overload, aluminum toxicity, or a metastatic tumor.

Slide 8:

There are several rare genetic disorders of PTH synthesis and action. Familial isolated hypoparathyroidism is caused by mutations to one of several genes that are responsible for PTH synthesis and secretion. These mutations can be inherited as autosomal dominant, autosomal recessive, or X-linked recessive. Loss of function mutations in the calcium sensing receptors, mutations in the autoimmune regulator gene, or mutations in the PTH gene are all components of familial isolated hypoparathyroidism. Congenital hypoparathyroidism refers to infants who are born without parathyroid tissue, the ability to make PTH, or without properly functioning glands. Autosomal dominant hypocalcemia types 1 and 2 are caused by gain of function mutations of the calcium sensing receptors. These mutations increase the activity of the receptors without binding plasma calcium, leading to an inappropriate inhibition of PTH secretion even when patients have hypocalcemia. DiGeorge syndrome is an autosomal dominant disorder caused by a deletion in chromosome 22, which affects the development of the skull, thymus, and parathyroid. Patients with DiGeorge syndrome often have hypoparathyroidism as well as several birth defects including congenital heart disease, defects in the palate, learning disabilities, and mild differences in facial features.

Slide 9:

PTH resistance is a type of hypoparathyroidism in which the kidneys and skeleton fail to respond to increased PTH levels. Therefore, a patient with PTH resistance often has hypocalcemia, hyperphosphatemia, and PTH concentrations above the reference interval. Because the disorder has the features of hypoparathyroidism, but with increased PTH concentrations, PTH resistance is also known as pseudohypoparathyroidism, or PHP. Type 1 PHP is caused by a deficient cyclic AMP response to increased PTH. Type 2 is caused by a defect in the cell's response to increased cyclic AMP, also known as cyclic AMP resistance. Type 1 and type 2 PHP are distinguished from one another with the injection of exogenous PTH. If a patient has type 1, he or she will not elicit a cyclic AMP response, and subsequently will not have urinary cyclic AMP and phosphate. However, if a patient has type 2, injection of exogenous PTH will elicit an increase in urinary cyclic AMP without phosphaturia.

Slide 10:

Along with low calcium and increased phosphate and PTH, patients with PHP have distinct phenotypic features. This includes a heart-shaped or round face, shortened 4^{th} and 5^{th} metacarpals, obesity, short stature, and varying degrees of developmental delay or mental retardation. If patients have this phenotype without the disordered calcium and phosphate metabolism, this disorder is called pseudopseudohypoparathyroidism, or PPHP, which is inherited from a father with PHP.

Slide 11:

The reversible impairment of PTH secretion can be caused by magnesium deficiency. Hypomagnesemia impairs PTH secretion. Typically, the parathyroid gland responds to low magnesium concentrations with an increase in PTH secretion, but as magnesium depletion progresses, the ability of the parathyroid to secrete PTH becomes impaired. Hypomagnesemia causes resistance to PTH. Renal resistance, such as impaired phosphaturia and cyclic AMP generation, as well as skeletal resistance in the form of decreased calcemic effects, has been seen in patients with magnesium deficiency. Administration of magnesium to patients with hypomagnesemia results in an immediate rise in serum PTH concentrations.

Slide 12:

Transient hypoparathyroidism can also occur in immature newborns, infants of diabetic mothers, during neonatal illnesses, and in kids and adults with severe illness, stress, sepsis, or surgery. The parathyroid function should recover after the acute illness has passed.

Slide 13:

Hypoparathyroidism is diagnosed by measuring calcium, albumin (to confirm that the low calcium concentrations are not due to hypoproteinemia), phosphate, and PTH in the blood. Patients with hypoparathyroidism will typically have decreased calcium, normal albumin, increased phosphate, and decreased PTH. Hypomagnesemia must be ruled out in the diagnosis of hypoparathyroidism. If PTH is normal or high in the setting of low serum calcium and high serum phosphate, pseudohypoparathyroidism should be considered.

Slide 14:

The treatment of hypoparathyroidism is directed at relieving the symptoms and normalizing calcium and phosphate blood concentrations. Therefore, patients with hypoparathyroidism often

take calcium and vitamin D supplements. There is also an FDA-approved once-daily injection of exogenous PTH. Due to its risk of bone cancer, this drug is only available to patients whose calcium concentrations cannot be controlled with calcium and vitamin D supplements. Calcium-rich and phosphate-poor diets are also recommended for individuals with hypoparathyroidism.

Slide 15:

In summary, hypoparathyroidism is a deficiency in PTH secretion and action. It can be caused by parathyroid destruction, genetic disorders of PTH synthesis and action, PTH resistance, or reversible impairment of PTH secretion. The clinical signs and symptoms of hypoparathyroidism often reflect the symptoms of hypocalcemia, and measuring the calcium, phosphate, and PTH concentrations in the blood are essential to establishing a diagnosis and in monitoring treatment.

Slide 16: References

Slide 17: Disclosures

Slide 18: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on “Hypoparathyroidism.”

QUESTION BANK TEMPLATE

Field	Instructions	
Stem	Write one question *Refer to Guide for Presenters for guidance (Page 5)*	Which of the following is a typical laboratory finding with patients with pseudohypoparathyroidism?
Responses	Provide 5 responses *Refer to Guide for Presenters for guidance (Page 5)*	A. High serum calcium B. High serum PTH C. Low serum phosphate D. High urine phosphate E. High urine calcium
Answer	Indicate one correct response	B. High serum PTH
Discussion	Provide a discussion of the correct response with main points explaining why it is the best choice	Patients with PHP have PTH resistance. Therefore, his or her PTH is increased, but the person displays all of the features of a patient with hypoparathyroidism – low serum calcium, high serum phosphate, low urine phosphate, and low urine calcium.
Source(s)	Provide the source(s) of information for further study *Refer to Guide for Presenters for full citation formatting (Page 3)*	Winter W, Harris N. Calcium Biology and Disorders. In: Clarke W, editor. Contemporary Practice in Clinical Chemistry. 2nd Ed. Washington DC: AACC Press; 2011. p. 505-526.
Difficulty	Select one level of difficulty: *Easy, intermediate, advanced*	Easy
Category	Select one category (*Refer to list in Guide for Presenters - Page 6)*	Chemistry
Sub-category	Select one sub-category (*Refer to list in Guide for Presenters - Page 6)*	Chemistry-Endocrinology

Keywords	Include at least 1-2 keywords *Keywords should describe a subtopic to the sub-category selected. Examples include, thyroid, electrolytes, diabetes, pregnancy, etc.*	Hypoparathyroidism, pseudohypoparathyroidism
Field	**Instructions**	
Stem	Write one question *Refer to Guide for Presenters for guidance (Page 5)*	Which of the following is a result of PTH secretion?
Responses	Provide 5 responses *Refer to Guide for Presenters for guidance (Page 5)*	A. Decreased calcium reabsorption in the kidney B. Decreased urinary phosphate wasting C. Decreased resorption of calcium and phosphate from the bone D. Increased 1,25$(OH)_2$ vitamin D production E. Increased 25(OH) vitamin D production
Answer	Indicate one correct response	D. Increased 1,25$(OH)_2$ vitamin D production
Discussion	Provide a discussion of the correct response with main points explaining why it is the best choice	PTH increases the expression of 1α-hydroxylase, which converts inactive 25(OH) vitamin D into active 1,25$(OH)_2$ vitamin D. PTH secretion increases calcium reabsorption and urinary wasting in the kidney and increases the resorption of calcium and phosphate from the bone.
Source(s)	Provide the source(s) of information for further study *Refer to Guide for Presenters for full citation formatting (Page 3)*	Winter W, Harris N. Calcium Biology and Disorders. In: Clarke W, editor. Contemporary Practice in Clinical Chemistry. 2nd Ed. Washington DC: AACC Press; 2011. p. 505-526.
Difficulty	Select one level of difficulty: *Easy, intermediate, advanced*	Easy

Category	Select one category (*Refer to list in Guide for Presenters - Page 6)*	Chemistry
Sub-category	Select one sub-category (*Refer to list in Guide for Presenters - Page 6)*	Chemistry-Endocrinology
Keywords	Include at least 1-2 keywords *Keywords should describe a subtopic to the sub-category selected. Examples include, thyroid, electrolytes, diabetes, pregnancy, etc.*	Hypoparathyroidism

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PEARLS OF LABORATORY MEDICINE

Hypoparathyroidism

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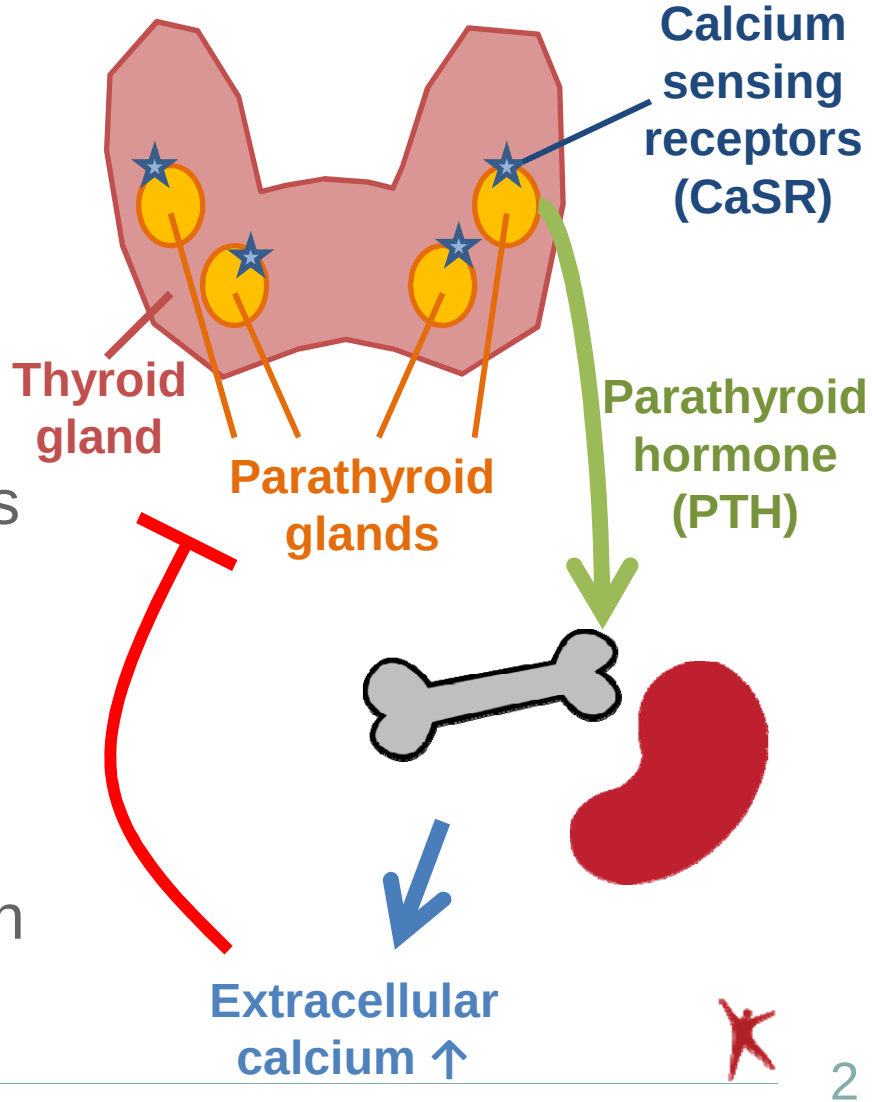
DOI:

CCTC Clinical Chemistry Trainee Council

Parathyroid Hormone Secretion

1) CaSR on parathyroid glands sense low blood calcium
2) PTH is secreted from parathyroid glands
3) PTH binds the PTH receptors on bone and kidney
4) Calcium released into cytoplasm
5) High calcium in blood downregulates PTH secretion



PTH Action in the Kidney and Bone

- In the kidney:
  - Increases calcium reabsorption
  - Inhibits phosphate reabsorption
  - Increases urinary phosphate wasting
  - Activates the conversion of inactive vitamin D to active vitamin D
- In the bone:
  - Increases the resorption of calcium and phosphate
- **Overall, PTH secretion = ↑ Calcium & ↓ Phosphate in blood**

Definition of Hypoparathyroidism

- A condition in which the body has low PTH secretion and/or action.
- PTH blood concentrations are inappropriately low for patients with hypocalcemia

Signs and Symptoms of Hypoparathyroidism

- Muscle involvement
  - Parasthesia
  - Muscle cramps
  - Muscle weakness
  - Twitching
  - Tetany
- CNS abnormalities
  - Depression
  - Altered mental status
  - Seizures
  - Coma
- Cardiac abnormalities
  - Arrhythmias
  - Hypotension
  - Heart failure
  - Respiratory failure
  - Cardiac abnormalities
- Respiratory Failure
  - Bronchospasm
  - Laryngospasm

Causes of Hypoparathyroidism

- 4 categories:
  - Parathyroid destruction
  - Genetic disorders
  - PTH resistance
  - Reversible impairment of PTH secretion

Hypoparathyroidism Caused by Parathyroid Destruction

- Parathyroidectomy
- Irradiation of parathyroid glands
- Autoimmune illness:
  - Autoimmune hypoparathyroidism
  - Type 1 autoimmune polyglandular syndrome
- Infiltration of parathyroid:
  - Wilson's disease
  - Iron overload
  - Aluminum toxicity
  - Metastatic tumor

Hypoparathyroidism Caused by Genetic Disorders

- Familial isolated hypoparathyroidism
  - Loss of function mutations in CaSR
  - Mutations in autoimmune regulator gene
  - Mutations in PTH gene
- Congenital hypoparathyroidism
- Autosomal dominant hypocalcemia
  - Gain of function mutations in CaSR
- DiGeorge syndrome
  - Deletion of Ch.22

Hypoparathyroidism Caused by PTH Resistance

- PTH resistance – when the body does not respond to increased PTH
- Pseudohypoparathyroidism (PHP) – increased PTH with hypoparathyroidism signs and symptoms
- Type 1 PHP – defective cAMP
  - Inject exogenous PTH = urine cAMP ↓, urine phosphate ↓
- Type 2 PHP – cAMP resistance
  - Inject exogenous PTH = urine cAMP ↑, urine phosphate ↓

Signs and symptoms of PHP

- Calcium ↓, Phosphate ↑, PTH ↑
- Heart-shaped or round face
- Shortened 4th and 5th metacarpals
- Obesity
- Short stature
- Developmental delay or mental retardation

- Pseudopseudohypoparathyroidism – PHP phenotype without calcium, phosphate, and PTH abnormalities

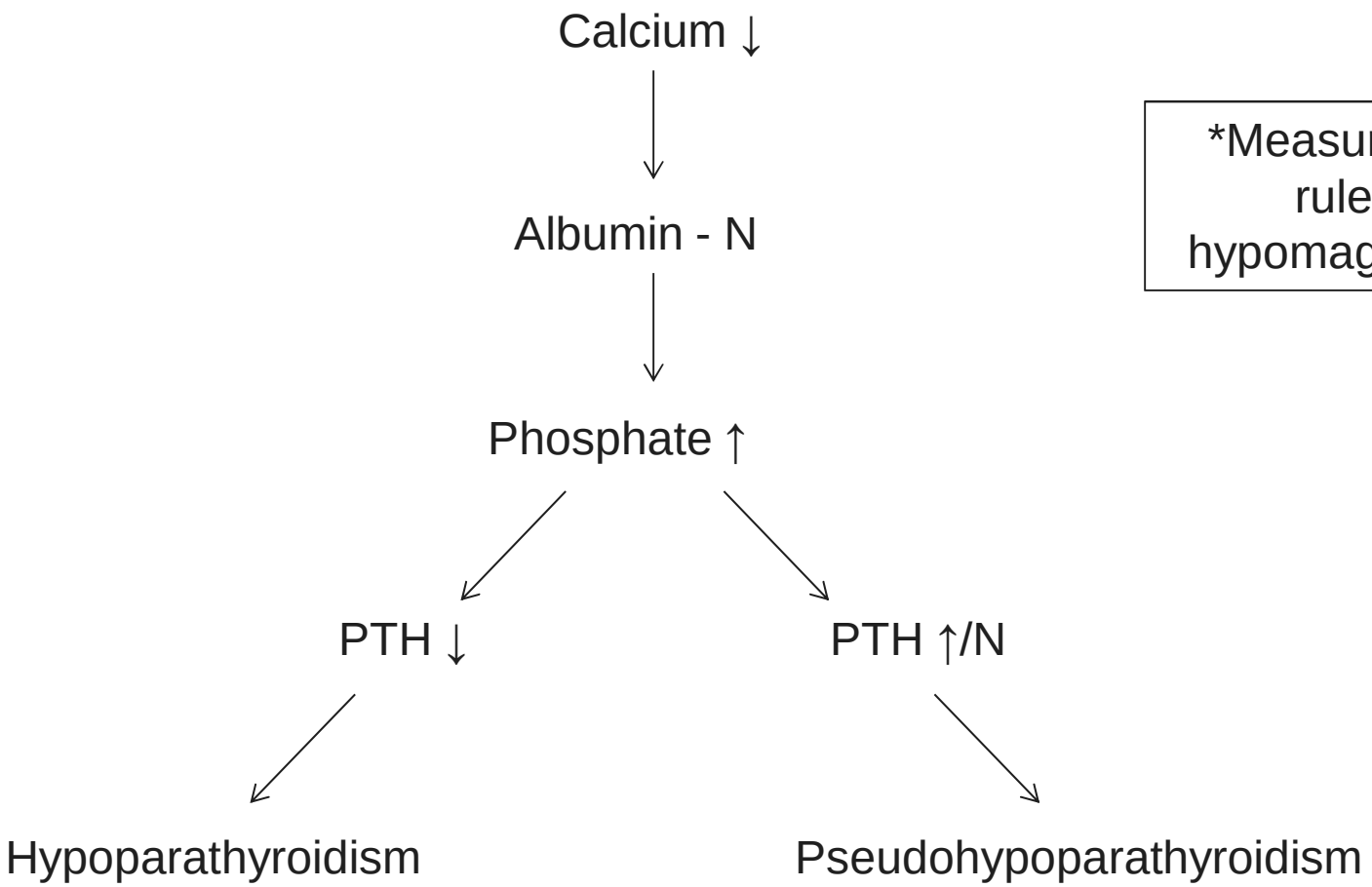
Hypoparathyroidism Caused by Reversible Impairment of PTH Secretion

- Hypomagnesemia impairs PTH secretion by causing PTH resistance
  - Renal resistance = urine cAMP ↓, urine phosphate ↓
  - Skeletal resistance = decreased calcium reabsorption from bone
- Magnesium administration will result in an immediate rise in serum PTH concentrations

Transient hypoparathyroidism

- Immature newborns
- Infants of diabetic mothers
- Neonatal illnesses
- Kids and adults with severe illness, stress, sepsis, or surgery

Diagnosis of hypoparathyroidism



*Measure Mg to rule out hypomagnesemia

Treatment of Hypoparathyroidism

- Calcium supplements
- Vitamin D supplements
- Exogenous PTH
- Calcium-rich and phosphate-poor diet

Summary

- Hypoparathyroidism – deficiency in PTH secretion and action in the setting of hypocalcemia
- Causes:
  - Parathyroid destruction
  - Genetic disorders
  - PTH resistance
  - Reversible impairment of PTH secretion
- Signs and symptoms reflect the body's response to low calcium
- Diagnose and monitor with regular measurements of blood calcium, phosphate, and PTH

References

1. Fraser W. Bone and Mineral Metabolism. In: Rafai N, Horvath A, Wittwer C, editors. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th Ed. St. Louis (MO): Elsevier; 2018. p.1422-1491.
2. Winter W, Harris N. Calcium Biology and Disorders. In: Clarke W, editor. Contemporary Practice in Clinical Chemistry. 2nd Ed. Washington DC: AACC Press; 2011. p. 505-526.
3. Rude R. Magnesium Deficiency: A Cause of Heterogeneous Disease in Humans. J. Bone Miner. Res 1998; 13:749-759

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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