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# Infantile Nephropathic Cystinosis
# STANDARDS OF CARE

## A Reference for People with Infantile Nephropathic Cystinosis, their Families, and Medical Team

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# Preface

The Cystinosis Standards of Care were written to help individuals with infantile nephropathic Cystinosis, their families, and their medical team. The information presented here is intended to add to conversations with physicians and other health care providers. No document can replace individual interactions and advice with respect to treatment.

One of our primary goals is to give affected individuals and their families greater confidence in the future. With early diagnosis and appropriate treatment, there is more hope today for families with Cystinosis than ever before. Research has led to better methods of diagnosis and treatment. Knowledge is increasing rapidly by virtue of the open sharing of information throughout the world among families, health professionals and the research community.

We acknowledge the important contributions to the Standards of Care of Dr. Galina Nesterova and Dr. William Gahl of the National Institutes of Health and the members of the Cystinosis Research Network's Medical and Scientific Review Boards.

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The Cystinosis Research Network is an all-volunteer, non-profit organization dedicated to supporting and advocating research, providing family assistance and educating the public and medical communities about Cystinosis. The Cystinosis Research Network's vision is the acceleration of the discovery of a cure, development of improved treatments and enhancement of quality of life for those with Cystinosis. We are a private, nonprofit 501(c)(3) corporation, Federal Tax ID 04-3323789.

***Disclaimer***
*The standards of care are intended to add to, not replace, conversations between the parent or patient and a physician, as the specific details and the patient's total health situation needs to be considered in making the final decisions about treatment. We hope that the standards of care will empower you to be a better partner in your child's or your own care, and will facilitate constructive conversations between you and your physician.*

# Contents

# Infantile Nephropathic Cystinosis Standards of Care

## Overview

Cystinosis is a rare inherited lysosomal storage disorder with:

- Deficiency of the lysosomal membrane transporter protein - cystinosin
- Reduced efflux of the amino acid cystine from lysosomes due to mutated cystinosin
- Accumulation of variable amounts of cystine
- Cellular and tissue dysfunction
- An incidence of one in 100,000-200,000 with autosomal recessive inheritance
- A prevalence of 500-600 children in the USA, with ~ 20 new cases each year
- Classic (Infantile) Nephropathic Cystinosis is the most common and most severe form
- ~ 5% of all chronic renal failure in children is accounted for by Nephropathic Cystinosis
- A typical presentation of failure to thrive, acidosis, renal tubular Fanconi's syndrome, muscle hypotonia, rickets, polyuria, polydypsia, photophobia, and renal failure at age 10 years

## Diagnosis

- The diagnosis of cystinosis is suggested by finding renal tubular Fanconi's syndrome
- The diagnosis is confirmed by findings of
  **a)** Typical corneal cystine crystals on slit lamp examination;
  **b)** Increased cystine content of leukocytes;
  **c)** CTNS mutations (per request)
- Targeted mutation analysis makes the diagnosis if 2 CTNS mutations are identified; CTNS is the only gene associated with cystinosis
  - Targeted mutation analysis for a common 57-kb deletion and/or the panel of CTNS mutations optimized for the French-Canadian population may be performed first
  - If neither one or no mutation in CTNS is identified, sequence analysis of the entire coding region is performed
  - Mutation analysis is commercially available

## Care for Early Complications

### • Cystine Depleting Therapy

- Cysteamine bitartrate (Cystagon® or Procyzbi®) - standard treatment for cystinosis
- Cystagon® is taken orally every six hours, 60 to 90 mg of free base per kg per day (1.3 to 1.95 g/m 2 per day), adult dose is 500 mg free base every six hours
- The recommended starting dosage of Procysbi® for cysteamine-naïve patients is 0.2 to 0.3 grams/m2 per day divided into two doses given every 12 hours. A titration period of 4 to 6 weeks starting at 1/6 to 1/4 of the maintenance dose helps reduce the risk of side effects
- Both preparations of cysteamine bitartrate max dose should not exceed 1.95g/m2/day
- Side effects include foul odor, headache, diarrhea, gastrointestinal upset, and unpleasant taste, contributing to non-compliance
- It is critical to maintain an appropriate dose of cysteamine
- Cysteamine has proven effective in delaying renal failure, enhancing growth, preventing hypothyroidism, and preventing late complications (see below). Cysteamine is not a cure for cystinosis
- Cystinosis results in the accumulation of cysteamine crystals in the cornea. Crystal deposition can be halted, and accumulated crystals dissolved, by frequent use of cysteamine eye drops (Cystaran®). Effective therapy is often achieved by dosing 8-10 times daily.

### 1. Renal Tubular Fanconi Syndrome

- Cystinosis is the most common cause of renal Fanconi syndrome in childhood
- The Fanconi syndrome appears at ~ 6 months
- Fanconi Syndrome presentation:
  - Polydipsia, polyuria, dehydration and hyperchloremic metabolic acidosis
  - Urinary losses of water (2-6 liters/day), sodium, potassium, bicarbonate, calcium, phosphate, magnesium, glucose, amino acids, tubular protein including ß2-microglobulin, and carnitine
  - Hypophosphatemia leading to rickets
  - Proteinuria in the nephrotic range
  - Hypercalciuric hypocalcemia, sometimes with tetany
  - Hypokalemia with risk of cardiac dysfunction
  - Hypercalciuria and hyperphosphaturia leading to medullary nephrocalcinosis
- Cystine crystals are present in macrophages, epithelial cells and epithelial lamina of the kidney

### Treatment of Fanconi Syndrome

- Free access to salt, water and bathroom privileges
- Supplementation with citrate (Polycitra, Bicitra) to alkalinize the blood; follow with CO2 levels
- Phosphate to cure the rickets; calcitriol to foster gastrointestinal phosphate absorption; follow with serum alkaline phosphatase
- Potassium, calcium, magnesium, carnitine supplementation as needed
- Careful attention to fluid and electrolyte replacement during acute illnesses
- Provide active oral or intravenous hydration
- Consider sodium acetate instead of sodium chloride
- Consider nasogastric tube placement, if there is no G-tube, for continuous oral hydration (Pedialyte, dextrose, saline, potassium)

## 2. Glomerular Involvement

- Some decline to a plateau in their renal function while others deteriorate rapidly
- End stage renal disease in untreated patients occurs by ~10 years
- End stage renal disease in patients treated with cysteamine occurs ~ 15-28 years
- Cystinosis glomeruli show focal and segmental glomerulosclerosis

## 3. Treatment of Renal Disease

- Evaluation by a nephrologist, renal function tests, electrolytes every 3 to 6 months (based on clinical need and KDOQI/Chronic Kidney Disease Clinical practice guidelines http://www.kidney.org/professionals/kdoqi/guidelines_commentaries.cfm)

### Treatment of Renal Failure

- Kidney transplant for end stage renal disease
- Hemodialysis and peritoneal dialysis temporizing measures
- When a live donor is available, pre-emptive transplantation is preferred
- Both living donor and cadaveric kidneys perform very well
  - Advances in anti-rejection medications have increased the pool of kidney donors
- Heterozygous relatives are acceptable donors
- Use of steroid-free immune suppression has been employed
- Retention of the native kidneys can result in persistence of Fanconi syndrome
- The donated kidney does not develop Fanconi syndrome

## 4. Growth Retardation, Osteodystrophy and Endocrine Involvement; Treatment

- Various degrees of renal damage, metabolic acidosis, metabolic bone disease, hypophosphatemic rickets, nutrient losses, and hypothyroidism contribute to profound growth retardation
- Apparent in the untreated child ~age 6 months
- Untreated, growth rate is 50%-60% of normal
- Hypophosphatemic rickets:
  - high fractional excretion of phosphate
  - normal vitamin D levels (levels can depend on degree of renal dysfunction)
  - elevated levels of serum alkaline phosphatase
- Osteomalacia, bone deformities, bone fragility and delayed ambulation
- Natural history of hypothyroidism in 50% by age 10 and 90% by age 30
  - Can be compensated, i.e., normal thyroxine but increased TSH
  - Can contribute to growth retardation

### Treatment of Growth Retardation

- Requires good nutrition, robust cystine depletion by cysteamine, adequate phosphate replacement (often 2-4 g/day) to prevent and heal hypophosphatemic rickets
  - Vitamin D to enhance gastrointestinal absorption of phosphate and calcium
  - Calcium supplementation for severe osteopenia
  - Low-dose thyroxine treatment
  - Growth hormone therapy beneficial for catch-up growth to normal height ( > 3 percentile)
  - Early therapy with cysteamine can obviate need for growth hormone
  - Physical therapy for hypotonia and recovering rickets

## 5. Gastrointestinal Complications and Nutrition; Treatment

- Nausea, vomiting and dysmotility are frequent
- A gastrostomy tube is recommended in patients not tolerating oral nutrition and oral medications
  - Evaluation by gastroenterologist for the surgical gastric or jejunostomy tube placement
  - Care providers for g-tube hygiene, prevention of gastric content leaks (zinc oxide, topical antibiotics)
- Intractable nausea alleviated by antinausea medications (Zofran)
- Patients with gastrointestinal reflux disease and side effects of cysteamine therapy benefit from medications such as omeprazole or ranitidine. Long term therapy with proton pump inhibitors has been associated with C. difficile infection which can exacerbate GI issues/ dehydration
- Formula intake is titrated for adequate calories
  - Gastrostomy tube feeding is reduced as oral intake increases
  - Oral feeding is encouraged
- Oral hydration is prescribed according to urinary losses and maintenance needs; electrolytes are needed to supplement enteral feeds; give gradually to prevent gastric overflow and vomiting
- Speech therapy and oromotor stimulation is beneficial

## 6. Corneal Cystine Crystals; Treatment

- Crystals usually present before age one year and always present by age 16 months – by slit lamp photography exam
- Can cause photophobia and later corneal erosions
- Slit lamp examination of the cornea showing typical cystine crystals is diagnostic for cystinosis
- Treatment with cysteamine eye drops
  - Age at initiation depends upon symptoms
  - 0.55% cysteamine solution (Cystaran®), every hour if possible. Effective therapy is often achieved by dosing 8/10 times daily.
  - May ameliorate the photophobia within weeks
  - Can dissolve corneal crystals in one to two years
- Avoid bright light, use dark glasses, lubrication with over-the-counter eye drops
- Corneal transplantation is very rarely required for band keratopathy, i.e., corneal calcifications

## 7. Intellectual Abilities:

Individuals with cystinosis should be encouraged to pursue educational/professional interests - a diagnosis of cystinosis should not be a reason to limit oneself. Provide support when/where needed.

- Generally normal cognition, with average school performance.
- May have impaired visual and spatial cognition
- Preserved language and intellectual function
- Distinctive behavioral and psychosocial difficulties due to:
  - chronic disease, ESRD/dialysis, prolonged hospitalizations, multiple therapeutic agents including steroids, missed school, family dynamics.
  - Some children demonstrate more intense mood swings or tantrums, in comparison to others of similar age
- Psychological support for child and family can be helpful
- Consider Early Intervention evaluation under age 3, and request school evaluation and Individualized Education Plan (IEP) if learning problems suspected, and 504 if school accommodations needed.
- Occupational therapy may be helpful

## 8. Vaccinations and Immunizations

- In pre-transplant patients, no contraindications; regular schedule is recommended
- In post-transplant patients with immunosuppressive therapy, live vaccinations (MMR and varicella) require consultation with an infectious disease specialist. Consult with your transplant nephrologist/infectious disease specialist if considering travel outside of your native country.

## 9. Transition to Adult Care

- Transitioning patients should demonstrate knowledge of cystinosis and all other conditions, all current treatments, labs done regularly, and how to contact providers.
- Transitioning must continue services uninterrupted with primary care and all specialists
- Cystinosis Research Network Transition Guide is a helpful resource and available at **www.cystinosis.org**

# Care For Adults With Infantile Nephropathic Cystinosis

## 1. Late-onset Systemic Abnormalities of Nephropathic Cystinosis

- Prior to renal transplantation and cystine-depleting therapy, lifespan was <10 years
- With these therapies, survival into the fifties revealed the complications of longstanding cystine accumulation in non-renal organs
- **Generalized vacuolar myopathy in 60% of individuals**
  - Leads to progressive muscle wasting and weakness starting in the hands
  - Causes oral motor dysfunction with swallowing and feeding difficulties later
  - On electromyography, shows a myopathic pattern
  - Causes extrinsic chest muscle impairment with extraparenchymal restriction leading to pulmonary insufficiency
  - Decreased FVC and FEV1 on routine pulmonary function tests
  - Night time BIPAP therapy can be of benefit for patients with restrictive lung disease as a result of cystinosis
- **Gastrointestinal Findings**
  - Reflux, dysmotility, esophagitis, gastric/duodenal ulcers, hepatomegaly with nodular regenerating hyperplasia of the liver and portal hypertension, exocrine pancreatic insufficiency, inflammatory bowel disease, bowel perforation, and peritonitis
- **Diabetes Mellitus**
  - Hyperglycemia is exacerbated by prednisone after transplantation; frequency 50–80% of young adults
  - Abnormal oral glucose tolerance tests
  - Many patients require insulin replacement therapy
- **Cardiovascular manifestations**
  - Arteriopathy with coronary calcifications
  - Obstructive atherosclerosis with hypercholesterolemia
  - End stage renal disease and renin-dependent hypertension
  - Dilated cardiomyopathy, rarely
  - Aortic aneurysms, rarely
  - Increased risk for myocardial infarction and neurovascular incidents
  - Can be exacerbated by dialysis
- **Metabolic bone disease** due to direct deposition of cystine crystals, mineral imbalance, and renal osteodystrophy
  - Bone mineral density as shown by dual energy X-ray absorptiometry (DEXA), can be significantly reduced
  - ~1/3 of patients had multiple fractures
- **Hypercoagulopathy and hypocoagulopathy** due to renal failure and platelet aggregation dysfunction
- **Central Nervous System Involvement**
  - Calcifications of basal ganglia and periventricular areas
  - Benign intracranial hypertension with non-absorptive hydrocephalus (pseudo tumor cerebri), may be treated with Diamox or Lasix
  - Parenchymal deterioration of central nervous system, rarely
  - Cerebral atrophy
  - Rare cerebrovascular incidents with paresis or pseudobulbar palsy

## 2. Late Ocular Complications

- Crystal deposition in anterior chamber, iris, ciliary body, choroid, fundus, and optic nerve
- Anterior segment problems
  - Crystals on the anterior lens surface, band keratopathy, peripheral corneal neovascularization, and posterior synechiae
- Posterior segment problems
  - Pigmentary retinopathy with degeneration of photoreceptors , impaired visual function in the late stage of the disease
  - Electroretinogram is used to confirm the retinopathy.

## 3. Monitoring of Adult Patients:

Requires team of specialists, including primary care, nephrologists, gastroenterologists, pulmonologists, endocrinologists, neurologists, ophthalmologists, rehabilitation services, psychologists, physical therapists. It is essential to encourage regular physical activity to help maintain cardiac, pulmonary, muscular, and bone health.

## 4. Laboratory Determinations

- Serum calcium, phosphate, alkaline phosphatase, bicarbonate, intact PTH, serum creatinine and creatinine clearance, thyroid panel, lipid studies, sex hormones, glucose intolerance test
- Urinary electrolytes and protein excretion – every 6 to 12 months
- Leukocyte cystine levels should be checked at least once a year for compliance and dose adjustment

## 5. Radiologic and Other Studies

(These studies are done at regular NIH visits, if adult with cystinosis is enrolled in adult protocol at NIH. Studies can also be done in home centers.)

- Modified barium videofluoroscopy (swallowing study) – if clinically indicated – every 2 years
- Electromyography – if clinically indicated – every 2 years
- Pulmonary function tests - every 2 years or as indicated. Start when patient can comply with instructions for pulmonary function testing, in conjunction with pulmonologist
- Renal ultrasound – once a year or as clinically indicated
- Bone X-rays and (DEXA) scans – if clinically indicated– once a year
- Brain magnetic resonance imaging (MRI) – every 2-5 years

## 6. Cysteamine Therapy Post-Transplant

The primary goal is to delay or reverse nonrenal organ deterioration

- Cysteamine treatment in the highest tolerated doses within the recommended range
- Long-term cysteamine treatment has shown efficacy in decreasing the frequency of:
  - Retinal deterioration, hypothyroidism, swallowing abnormalities, vascular calcifications, posterior eye segment defects, diabetes, myopathy, hypercholesterolemia
  - Deaths
- Several modalities of symptomatic therapy still apply to post-transplant patients
- For corneal cystine crystals, topical cysteamine hydrochloride solution 10–12 times per day

## 7. Reproduction

- Untreated patients nearly always exhibit late sexual maturation.
- In male patients not treated/undertreated with cysteamine:
  - Puberty starts at 16–17 years of age
  - Parenchymal tissue destruction and cystine accumulation within the testes
  - Patients develop hypergonadotropic hypogonadism
  - Low levels of testosterone and high levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)
  - Patients may benefit from testosterone supplements for secondary sexual characteristics
  - Infertility is common; no cystinosis patient is known to have fathered a child
  - The ability to have an erection remains intact
  - Consideration should be given for sperm banking or the use of donor sperm for infertile male adolescents and young adults
- In females with cystinosis not treated/undertreated with cysteamine:
  - Puberty is generally reached at 14–15 years of age
  - Ovulatory cycles and gonadal endocrine parameters are normal
  - Successful pregnancies and deliveries have been observed
  - Consider birth control options to avoid unplanned pregnancy
  - The pregnancies are at a higher risk for premature delivery and must be monitored closely
  - For women who are post-transplantation, the abdominal renal allograft creates mechanical issue
  - For women who have not undergone transplantation, fluid and electrolyte status require careful management.
- The teratogenicity of oral cysteamine in humans is not known; care must be taken to avoid exposing a fetus to cysteamine. It is a USFDA schedule ‘C” drug.

# Suggested Reading

## Gene Review Cystinosis

**http://www.ncbi.nlm.nih.gov/books/NBK1400/**

## Nephropathic Cystinosis:

Late Complications of a Multi-systemic Disease

**http://www.ncbi.nlm.nih.gov/pubmed/18008091**

## Cystinosis New England Journal of Medicine

**https://cystinosis.org/images/research/article-library/overview/NEJM%202002%20Gahl%20Schneider%20Theone.pdf**

## Nephropathic Cystinosis in Adults

**https://cystinosis.org/images/research/article-library/adults/Nephropathic%20cystinosis%20in%20adults%20NEJM.pdf**

# Glossary of Terms

**aortic aneurysm**: swelling of the aorta (largest artery in the body) usually from an underlying weakness

**arteriopathy:** a disease of the arteries

**atherosclerosis:** degenerative disease of the arteries characterized by patchy thickening of the arterial walls, caused by deposits of fatty material

**autosomal recessive inheritance:** one of several ways that a trait, disorder, or disease can be passed down through families; two copies of an abnormal gene must be present in order for the disease or trait to develop.

**band keratopathy:** band of calcium becomes deposited across the cornea that is grainy and whitish-gray in color

**benign intracranial hypertension**: also known as pseudotumor cerebri, increased pressure within the brain that appears to be, but is not, a tumor

**BIPAP (Bi-level Positive Airway Pressure):** Treatment for sleep apnea keeps the upper airway open by providing a flow of air delivered through a face mask worn while sleeping. The prescribed pressure alternates between two levels: one to breathe in (IPAP) and one to breathe out (EPAP). The air is pressurized by a small machine and delivered through plastic hosing to the mask.

**blepharospasm:** spasm of the muscle of the eyelids, causing the eyes to shut tightly

**cardiovascular:** relating to the heart and the blood vessels

**central nervous system:** the part of the nervous system that consists of the brain and spinal cord

**cerebral atrophy:** loss of brain tissue

**choroid:** layer of blood vessels and connective tissue between the sclera (white of the eye) and retina; part of the uvea and supplies nutrients to the inner parts of the eye

**ciliary body:** structure in the eye that releases a transparent liquid (called the aqueous humor) within the eye. The ciliary body also contains the ciliary muscle, which changes the shape of the lens when your eyes focus on something. This process is called accommodation.

**cognition:** mental act or process by which knowledge is acquired, including perception, intuition, and reasoning

**cornea:** clear front window of the eye, which transmits and focuses light into the eye

**cystinosin**: protein that is encoded by the CTNS gene

**cystinosis**: a rare, genetic metabolic disease that causes the amino acid cystine to accumulate in various organs of the body

**electromyography:** technique for recording the electrical activity of muscles; used in the diagnosis of nerve and muscle disorders

**encephalopathy:** degenerative disease of the brain, often associated with toxic conditions

**end stage renal disease:** the complete or almost complete failure of the kidneys to work; kidneys remove waste and excess water from the body.

**extraparenchymal:** not related to the essential elements of an organ

**endocrine:** relating to endocrine glands or the hormones secreted by them

**Fanconi syndrome**: urinary losses of essential nutrients including electrolytes (sodium, potassium, bicarbonate), minerals (calcium, phosphate, magnesium), glucose, amino acids, tubular protein including ß2-microglobulin, and water

**gastrostomy tube (g-tube):** tube inserted through a small incision in the abdomen into the stomach and is used for long-term nutrition

**glomerular:** pertaining to the glomerulus, a tiny structure in the kidney that filters the blood to form urine

**hemodialysis:** - dialysis of the blood to remove toxic substances or metabolic wastes from the bloodstream; used in the case of kidney failure

**hepatomegaly:** the condition of having an enlarged liver

**heterozygous:** possessing two different forms of a particular gene, one inherited from each parent

**hypercalciuric:** urinary excretion of excessive amounts of calcium

**hypercoagulopathy**: cause an increased tendency for clotting of the blood

**hyperglycemia:** an abnormally high level of glucose (sugar) in the blood

**hyperphosphaturia**: excess phosphate in the urine

**hypertension:** abnormally high blood pressure

**hypocalcemia:** reduced levels of calcium in the blood

**hypocoagulopathy:** decreased clotting of blood

**hypogonadism:** decreased production of sex hormones

**hypokalemia:** low levels of potassium in blood

**hypophosphatemia**: low levels of phosphate in the blood

**hypothyroidism:** decreased production of thyroid hormones

**hypotonia:** state of low muscle tone, often involving reduced muscle strength

**intractable nausea:** constant nausea

**iris:** colored part of the eye that helps regulate the amount of light that enters the eye

**jejunostomy tube (j-tube):** a feeding tube into the small intestine that bypasses the stomach

**lysosomal storage disorder:** diseases in which there is a genetic or acquired deficiency of an enzyme or transport protein so that one or more specific metabolic processes are not completed; resulting in an accumulation of metabolic products in the cellular lysosome

**medullary nephrocalcinosis**: calcium deposits in the kidney

**modified barium videofluoroscopy:** moving x-ray study that evaluates how food/liquid moves from the mouth to the esophagus; used evaluate, diagnose, and treat specific swallowing problems

**myocardial infarction**: destruction of heart tissue resulting from obstruction of the blood supply to the heart muscle

**nephrologist**: kidney specialist

**neurovascular:** relating to, or affecting both the nerves and the blood vessels

**ocular:** relating to the eye

**optic nerve:** connects the eye to the brain and carries the impulses formed by the retina

**osteodystrophy:** abnormal bone development usually due to kidney disease

**osteomalacia:** results from a deficiency in vitamin D or calcium and is characterized by a softening of the bones with accompanying pain and weakness

**parenchymal deterioration**: deterioration of the key elements of an organ essential to its functioning, as distinct from the capsule that encompasses it and other supporting structures

**paresis:** muscular weakness caused by nerve damage or disease

**peritoneal dialysis:** A dialysis technique that uses the patient's own body tissues inside the abdominal cavity as a filter. A plastic tube called a dialysis catheter is surgically placed through the abdominal wall, into the abdominal cavity. A special fluid is then flushed into the abdominal cavity and washed around the intestines. The intestinal walls act as a filter between this fluid and the bloodstream. By using different types of solutions, waste products and excess water can be removed from the body. This form of dialysis can be done either 'manually' or by machine at home, thereby avoiding hospitalization or receiving dialysis treatment at a dialysis center.

**photophobia:** painful oversensitivity to light

**polydypsia:** increased fluid intake because of excessive thirst

**polyuria**: abnormally large production or passage of urine

**proteinuria:** excess of proteins in the urine

**pseudobulbar palsy:** refers to a group of symptoms – including difficulty with chewing, swallowing, and speech, as well as inappropriate emotional outburst –- that accompany a variety of nervous system disorders

**pseudotumor cerebi**: also know as benign intracranial hypertension increased pressure within the brain that appears to be, but is not, a tumor

**pulmonary**: relating to, or affecting the lungs

**pulmonary function test (pft):** measure how well the lungs are working. PFTs gauge how the lungs are expanding and contracting (when a person inhales and exhales) and measure the efficiency of the exchange of oxygen and carbon dioxide between the blood and the air within the lungs.

**spatial cognition:** pertaining to the perception of the spatial relationships between objects and field of vision

**renal**: kidney

**rickets:** condition caused by serious vitamin D deficiency resulting in weak, soft bones, along with slowed growth and skeletal development

**tetany:** low blood calcium and ionized calcium and is characterized by spasms of the hands and feet, cramps, spasm of the voice box, and overactive neurological reflexes

**teratogenicity:** is any substance that can cause malformation of the fetus during pregnancy

**vacuolar myopathy:** structural change in skeletal muscle

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