Brigham and Women's Hospital
Founding Member, Mass General Brigham

A Missed Diagnosis

J. Carl Pallais, MD, MPH
Senior Physician, Division of Endocrinology, Diabetes and Hypertension
Associate Director, Internal Medicine Residency Program
Brigham and Women's Hospital
Assistant Professor, Harvard Medical School

J. Carl Pallais, MD, MPH

- MD - Johns Hopkins University School of Medicine
- MPH - Harvard School of Public Health
- Medicine Residency & Chief Resident - Massachusetts General Hospital
- Endocrine Fellowship - Massachusetts General Hospital
- Senior Physician - Brigham & Women's Hospital
- Assistant Professor of Medicine-HMS
  - Clinical focus: Calcium and Bone Disorders
  - Research focus: Endocrine Genetics

Disclosures

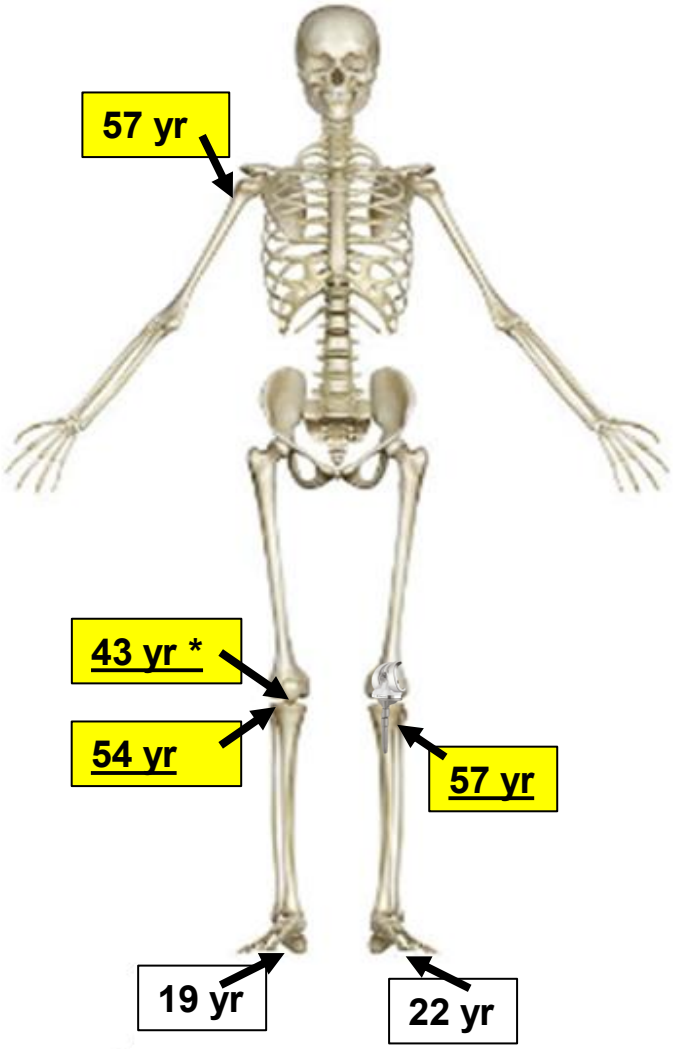
- UpToDate
  - Author
- Alexion Pharmaceuticals
  - Site PI for Global Hypophosphatasia Registry
- Ensho Health
  - Consultant
- Alesta Therapeutics
  - Consultant

Referral

59 yo F w h/o anxiety and pain syndrome who is nervous about starting on bisphosphonates prescribed by her PCP after recent fractures

Fracture History

- H/o recurrent fractures
  - 19 yo- R foot (step off bus)
  - 22 yo- L foot stress fracture (field hockey &tennis)
  - 43 yo- R patellar fracture (fall->ORIF w hardware failure)
  - 54 yo- R knee refracture (low trauma)
  - 56 yo L knee replacement (arthritis)
  - 57 yo fracture distal to TKR hardware
  - 57 yo R shoulder displaced comminuted fracture (trip & fall)



Past Medical History

- PMH:
  - **Anxiety**
  - **Migraines**
  - **Fibromyalgia**
  - **Arthritis requiring multiple arthroscopic procedures w chondrocalcinosis of L knee**
  - **Chronic joint pain**
  - **HTN**
  - **HLD**
- SH:
  - Lives w husband & son
  - 2-3 drinks/wk
  - No tob or illicits
  - Works as a project manager for research organization
- Meds:
  - Calcium Citrate 500 mg /d
  - Vitamin D3 1000
  - HCTZ 12.5
  - Diclofenac gel 4 topically
  - Meloxicam
  - Zolpidem
  - Tumeric root, Omega 3FA, elderberry extract, lactobacillus
- FH:
  - Irish ancestry & no fractures
    - Mother with cirrhosis (ETOH)
    - Father w arthritis, COPD, hip fracture
    - 1 sister healthy
    - Son –anxiety “on spectrum”

Menstrual & Dental History

- Menarche ~ 12 yo
- Regular periods
  - OCP for ~5 yrs for contraception
- 1 Pregnancy
- Menopause at 54
- No HRT

- No missing teeth
- Some fillings and periodontal disease but no root canals, crowns, or implants

Dietary Calcium Intake

- ½ cup soy milk/d, regular cheese
- CaCitrate 500 + vit D 1K

Physical Exam

- **Vital signs**:
  - **145/81**, 67, **200 lb**, 65 in, **BMI 33-** generalized obesity, not Cushingnoid
- **General:**
  - Well-appearing, no sweats or tremors
- **HEENT:**
  - EOMI, PERRL, no lid lag, proptosis, white sclera, VS full to confrontation
  - MMM, **several fillings**, no extractions/discoloration/atrophic anamel
  - Normal thyroid
- **Musc/skeletal:**
  - **Orthopedic scars,** good strength with slight muscle aches, no joint hypermobility
- **Neuro:**
  - CN intact, normal hearing, no tremors

Does this Patient Have Osteoporosis?

A. No, need labs prior to making a diagnosis
B. No, need DXA prior to making a diagnosis
C. Yes, and would start treatment
D. Yes, but need labs prior to starting treatment
E. Yes, but need DXA and FRAX score prior to starting treatment

Does this Patient Have Osteoporosis?

A. **No, need labs prior to making a diagnosis**
B. No, need DXA prior to making a diagnosis
C. Yes, and would start treatment
D. Yes, but need labs prior to starting treatment **(Technically correct)**
E. Yes, but need DXA and FRAX score prior to starting treatment

Need to rule out other explanation or metabolic bone disease, such as osteomalacia, with baseline lab:

- **Calcium, phos, alk phos, vitamin D, creatinine, CBC**

Osteoporosis Classification

- Osteoporosis
  - T score ≤ -2.5
  - Or presence of fragility fracture

→ **TREAT!**

- Osteopenia
  - T score: -1 to -2.5

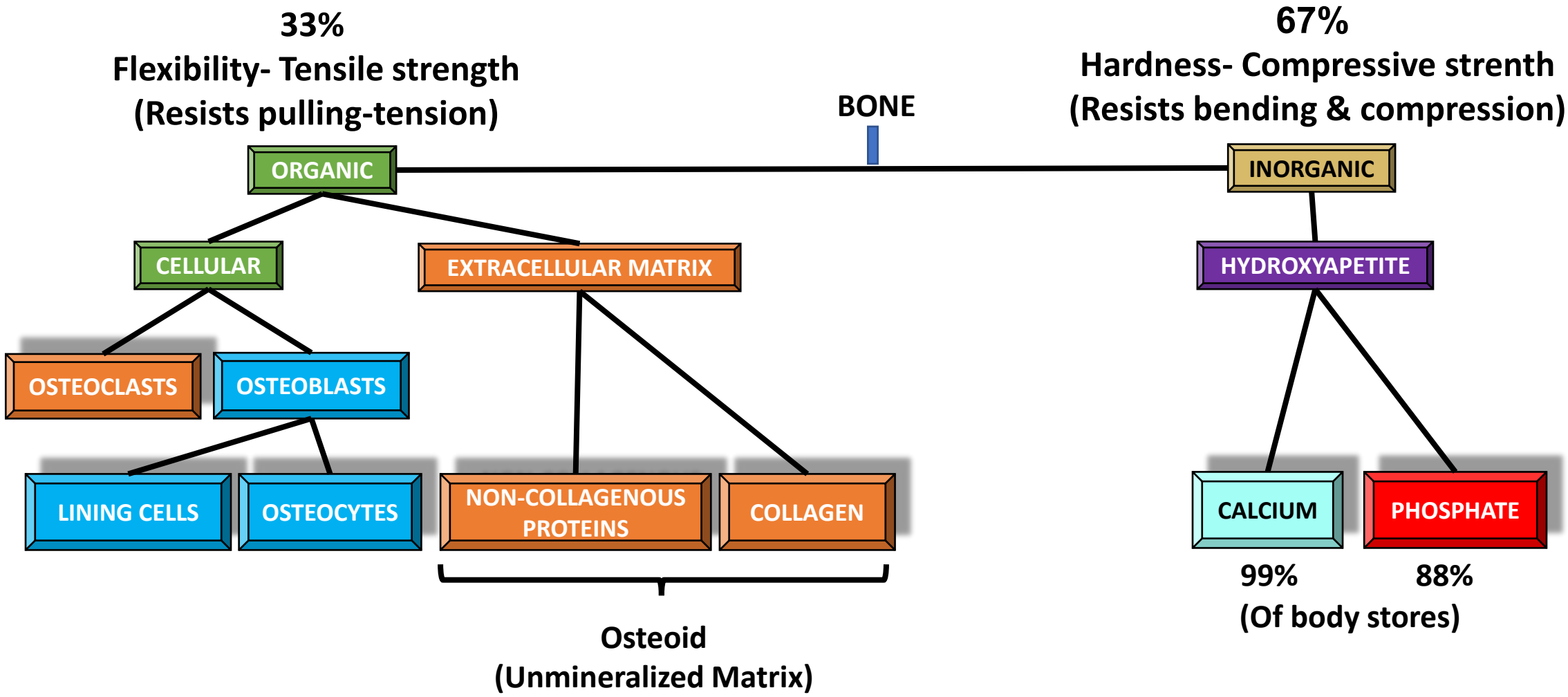
→ **Treat?**

FRAX Calculator

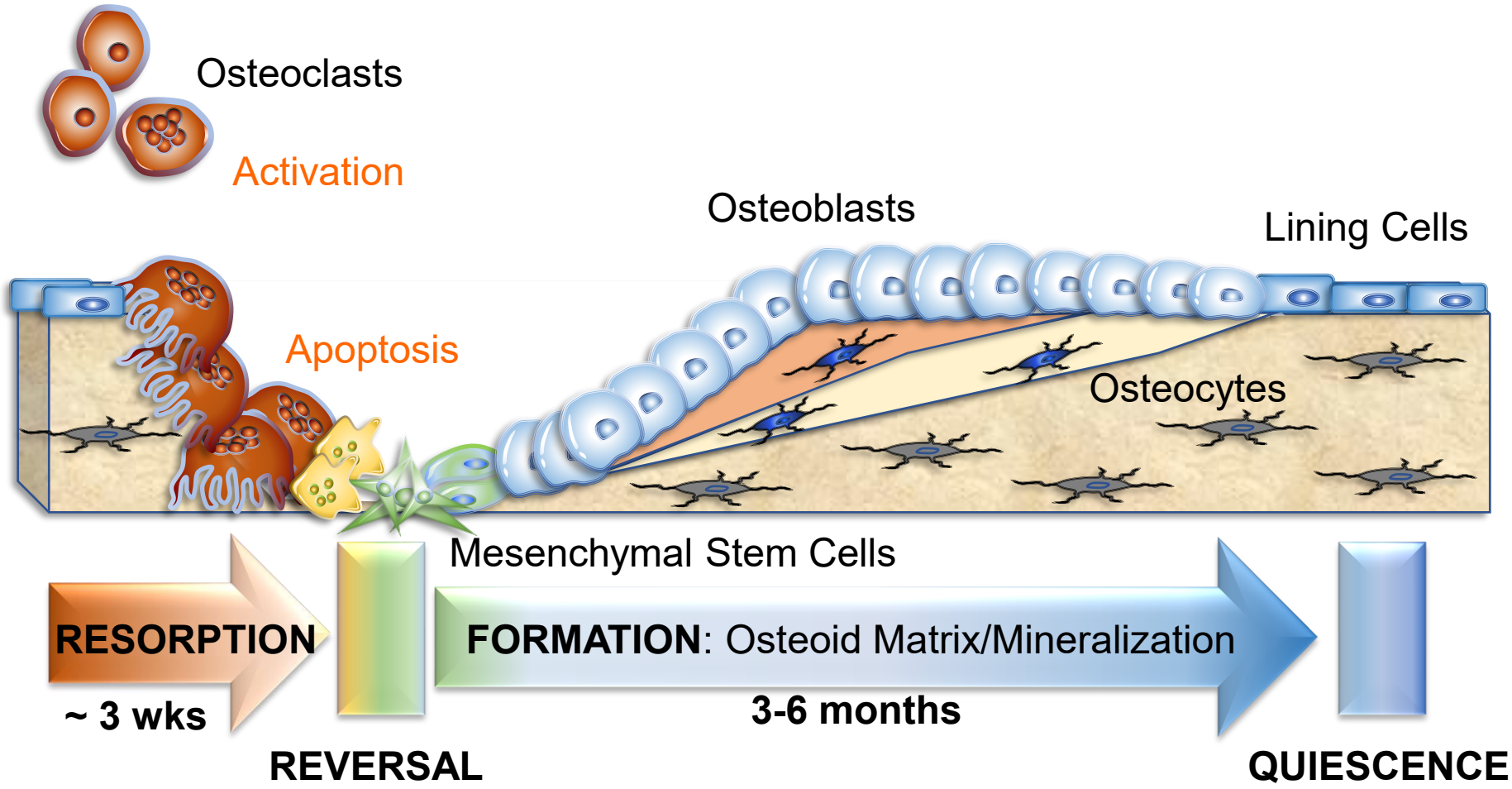
10 yr MOP ≥ 20%, hip frx ≥3%

Walker.JAMA.2025.

Bone Composition

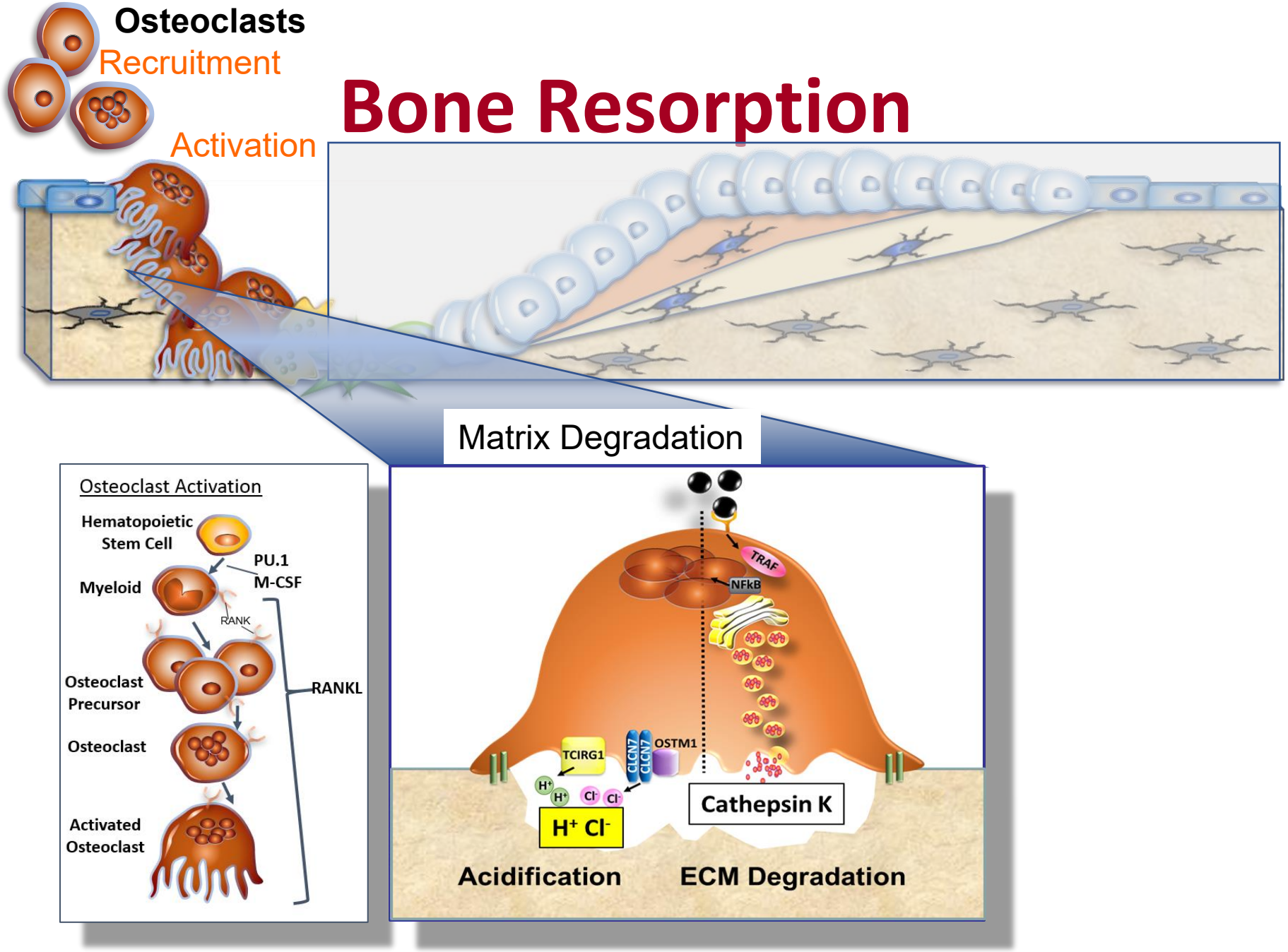


Normal Bone Remodeling

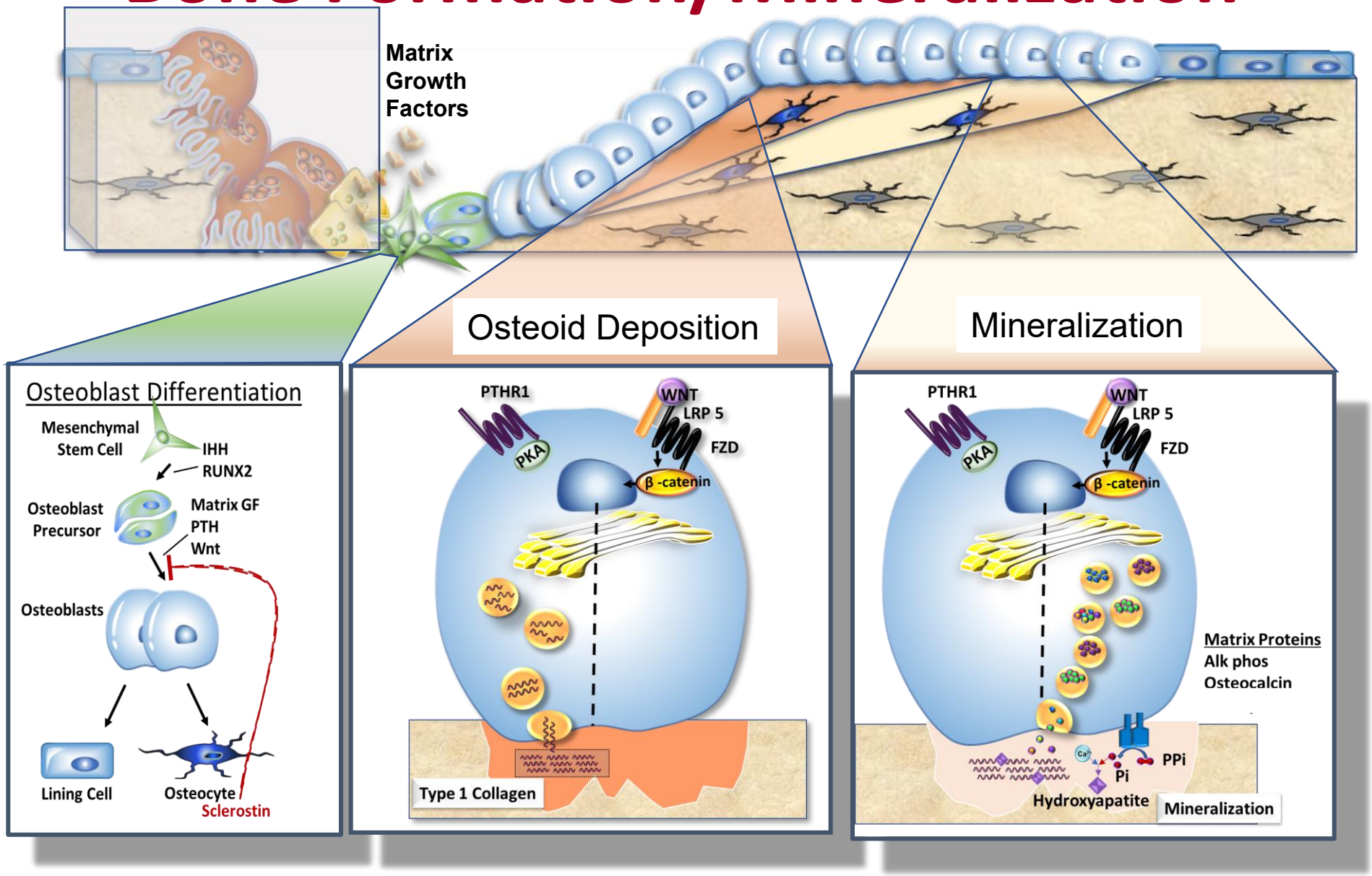


Eriksen.Bone Histomorphometry.1994.

Bone Resorption



Bone Formation/Mineralization

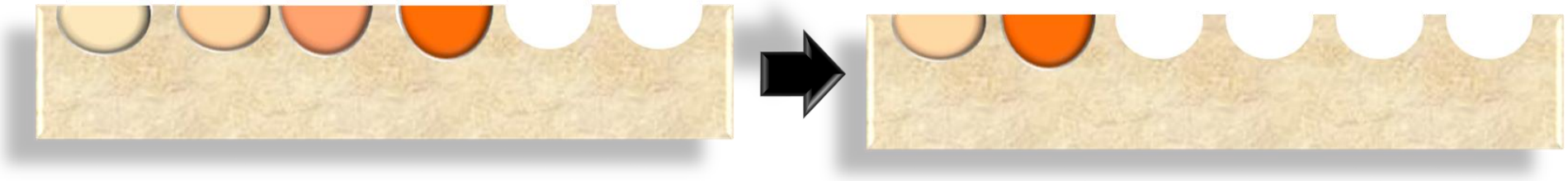


Bone Pathology

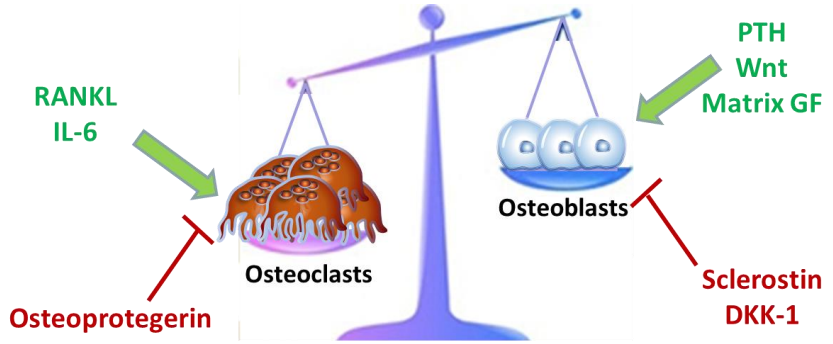
Multiple fractures

Osteoporosis/Osteopenia

Resorption > Formation



Normal Bone



Secondary Causes of Osteoporosis

- Hyperparathyroidism
- Estrogen deficiency
  - Delayed puberty
  - Early menopause
  - Hypogonadism
  - Aromatase inhibitors
- Glucocorticoid exposure
- Hyperthyroidism
- GH deficiency
- Malnutrition/eating do
- Malabsorption/Celiac dz
- Liver disease
- Renal disease
- Pulmonary disease
- Multiple myeloma
- Mastocytosis
- Inflammatory do (RA, etc)
- Immobility
- ETOH, tobacco, PPI, etc

Treatment

Anti-Resorptives

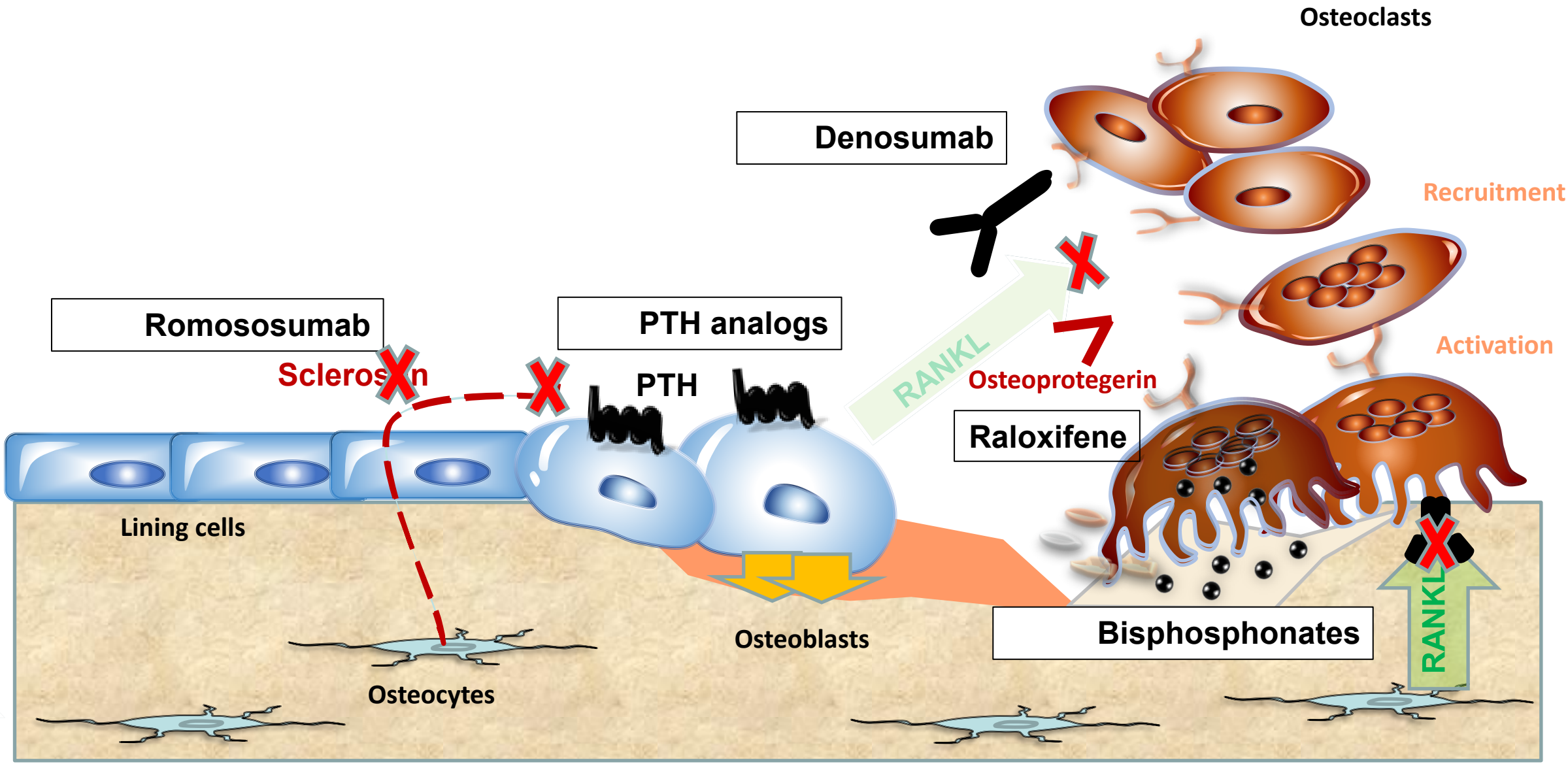
- Bisphosphonates
  - Alendronate (Fosamax)
  - Risdronate (Actonel)
  - Zoledronate (Reclast)
  - Ibandronate (Boniva)
- Denosumab (Prolia)

Anabolics

- PTH analogs
  - Teriparatide (Forteo)
  - Abaloparatide (Tymlos)
- Sclerostin inhibitors
  - Romosozumab (Evenity)

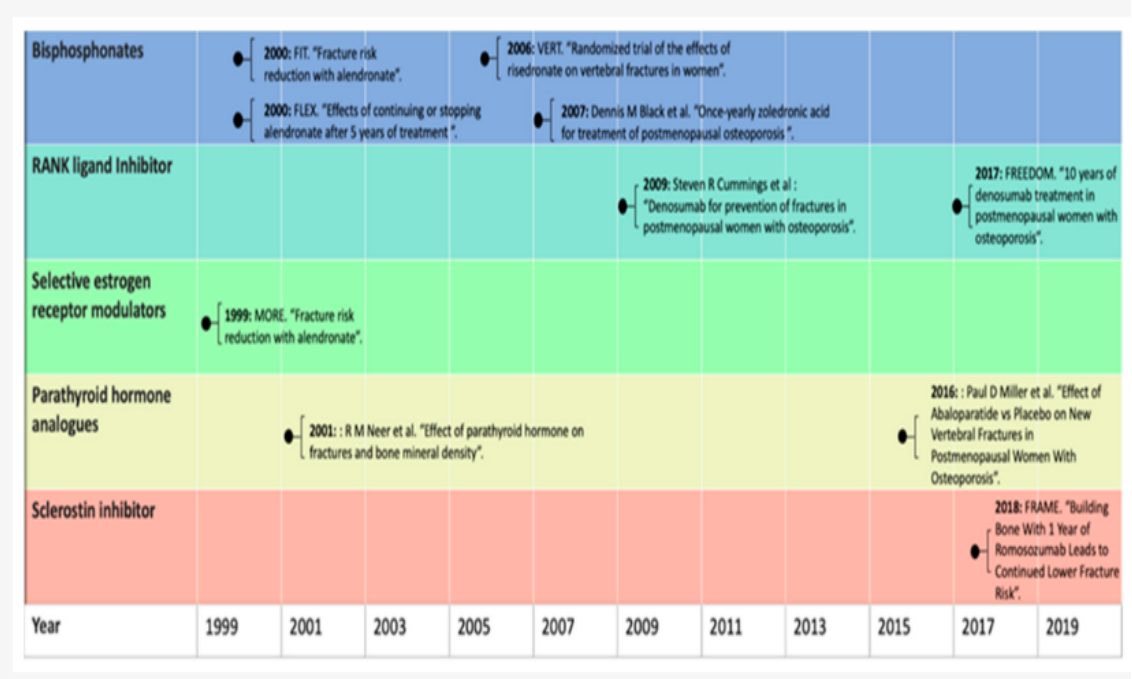
How do they work?

Mechanism of Action

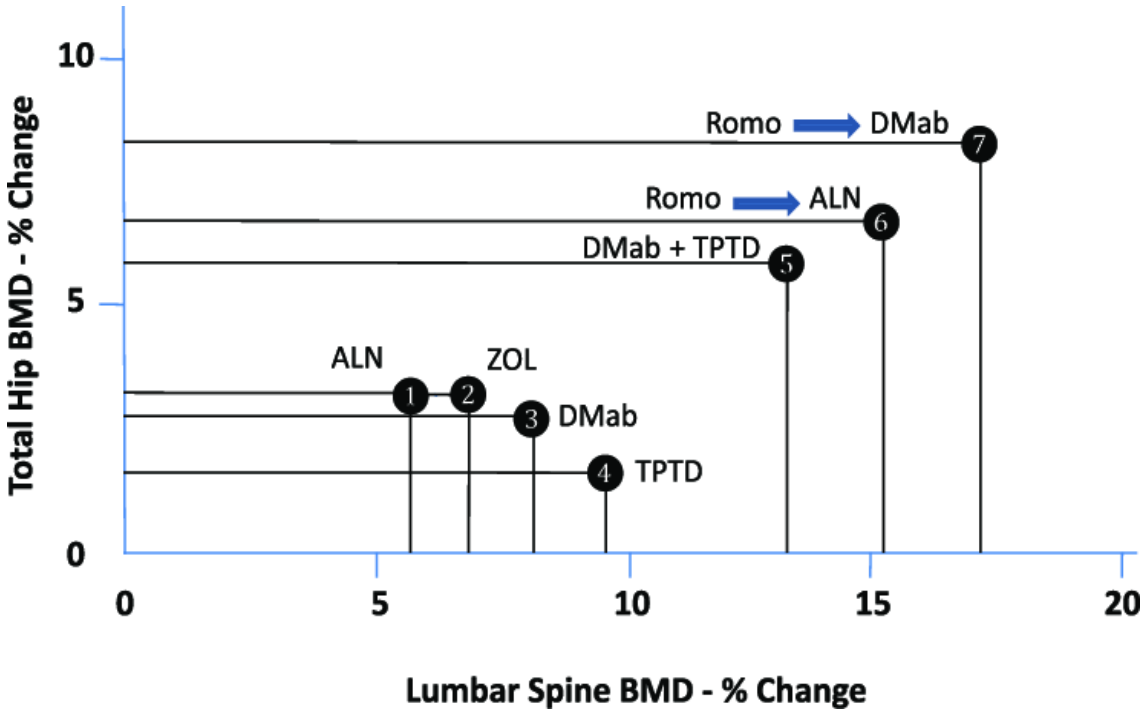


Effectiveness

Major Trials



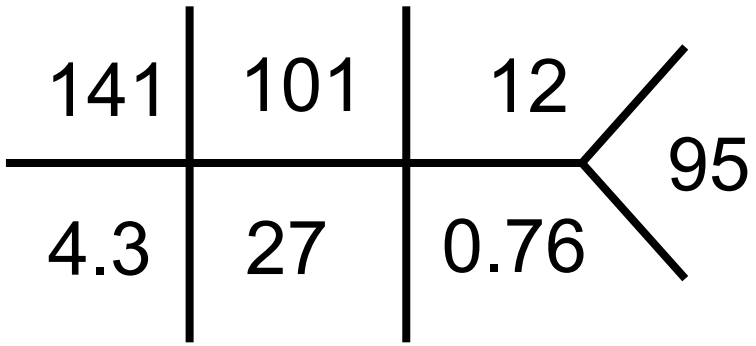
Treatment Effects

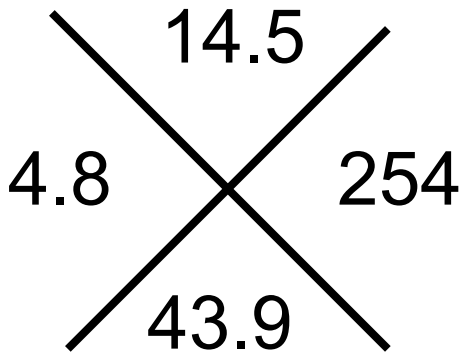


Ayub. J Clinical Med.2021

McClung. Osteoporosis & Sarcopenia.2018

Labs





Ca	10.1	
Alb	4.8	
Phos	4.0	
Vitamin D		34
PTH		34
24hr:	Ca	245 mg
	Crt	1.1 g
	TV	1.9 L

ALT	23
AST	21
Alk Phos	25
Bili	0.6
TSH	1.3
Tryptase	neg
SPEP	no M spike

BMD

Site	T Score	Z Score	Classification
AP Spine	-0.1	+1.1	Normal
L Femoral Neck	-0.7	+0.4	Normal
L Total Hip	+1.1	+1.9	Normal

Pt prescribed alendronate but was anxious about "possible side effects", especially with normal bone density

- **Fear of arthritis pain worsening**
- **ONJ was also a concern**

"Are there supplements that I can take instead?"

Bone Pathology

Multiple fractures

Normal Bone

Collagen Defect

Osteogenesis Imperfecta

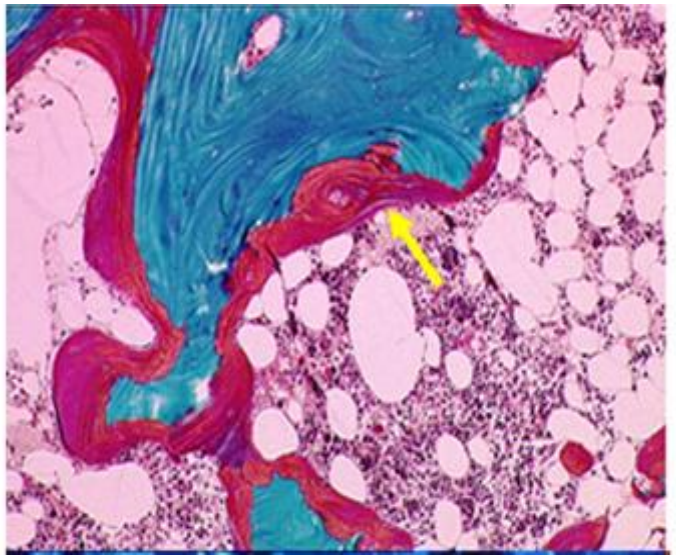
Osteoporosis

Resorption > Formation

Impaired Mineralization

Rickets/Osteomalacia

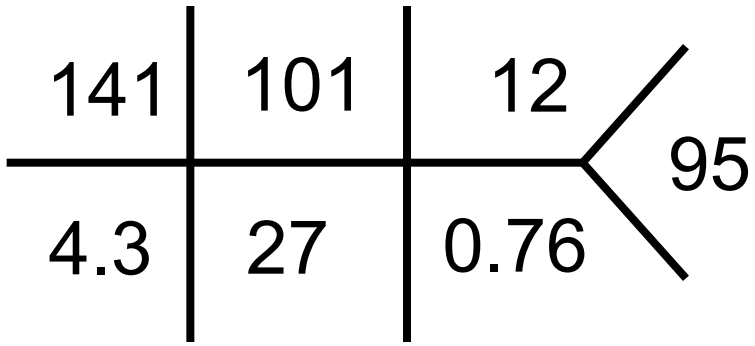
Conditions with Mineralization Defects

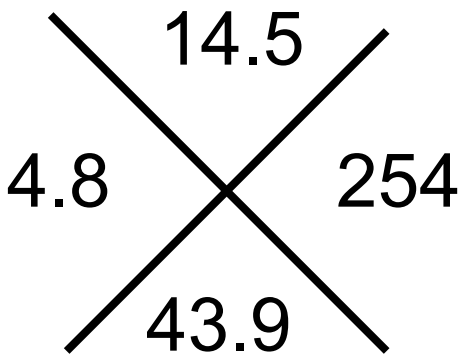


MINERALIZATION DEFECTS		Calcium	Phos	25vitD	1,25vitD	PTH	Alk Phos
Vit D Deficiency	25 vit D	Nl/-	Low/Nl	Low	Nl/+	High	High/Nl
	1,25 vit D	Nl/-	Low/Nl	Nl/-	Low	High	High/Nl
	Renal Failure	Nl/-	Nl/High	Nl	Low	High	Variable
Hypo-phosphatemia	Nutrition/GI	Nl/-	Low	Low/Nl	Nl	High	High/Nl
	Renal:FGF23	Nl/-	Low	Nl/-	Low	High	High
	Renal:Fanconi	Nl	Low	Nl	Nl/+	Nl	Nl
Hypophosphatasia		Nl/High	Nl/High	Nl	Nl	Nl	LOW

Berksethetal.Bone.2013; Michigami.Ann Pediatr Endocrinol Metab.2019

Labs





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24hr:	Ca	245 mg
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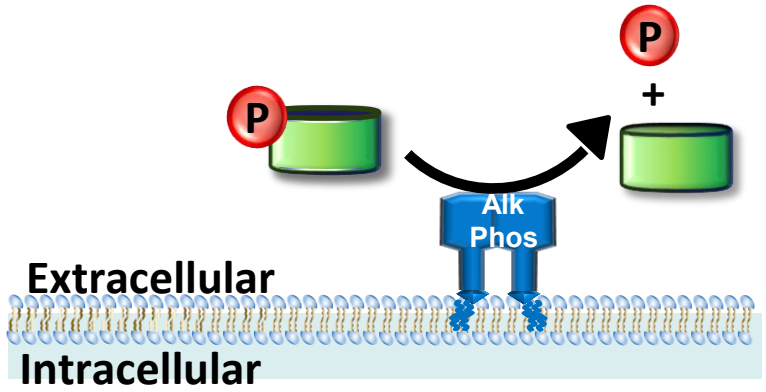
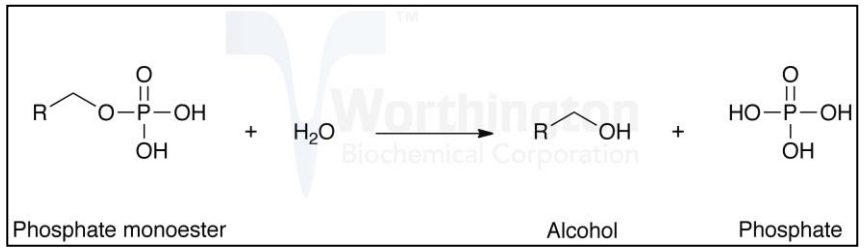
	TV	1.9 L

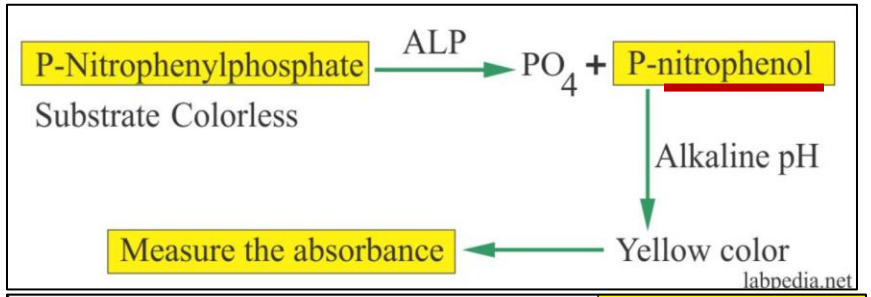
ALT	23
AST	21
Alk Phos	**25 (nl ≥ 35), 21-25 for decades**
Bili	0.6
TSH	1.3
Tryptase	neg
SPEP	no M spike

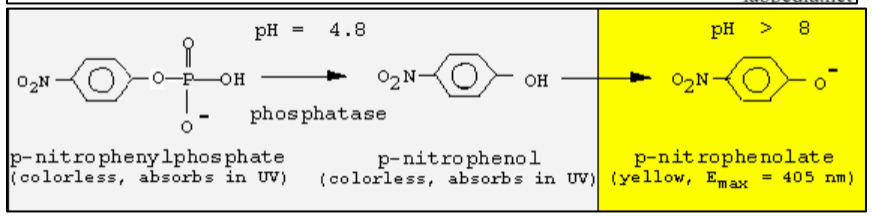
Alkaline Phosphatase



- Group of phosphatases
- Catalyze removal of a monoester phosphate from multiple substrates
- Optimal activity in alkaline environment
  - Clinical assay requires pH > 8
  - P-Nitrophenol –Phosphate (pNPP)
    - **Artificial** substrate in assay
- But normal **function is at physiologic pH**







pH >8

pNPP assay **CORRELATES** with physiologic ALP activity

Millan.Purinergic Signaling.2006; Vimalraj.Gene.2020; Fedde.Am J Hum Gen.1990; Graser.Int J Molec Sci.2021

Component of "Liver Function Test"

LFT Interpretation

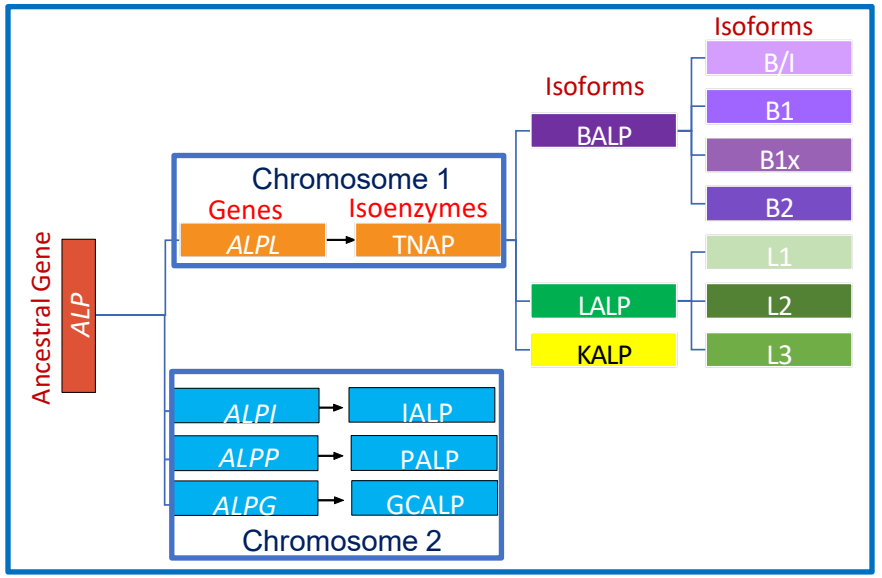
- Hepatocellular injury
  - ↑AST & ALT ± ↑ bili & Aϕ
    - If ↓ Aϕ- Wilson's
- Cholestasis
  - ↑ Bili & Aϕ ± ↑AST & ALT
- Infiltrative
  - ↑ Aϕ, near normal bili, AST & ALT

Bone Specific Component: ~20-60% of total Aϕ

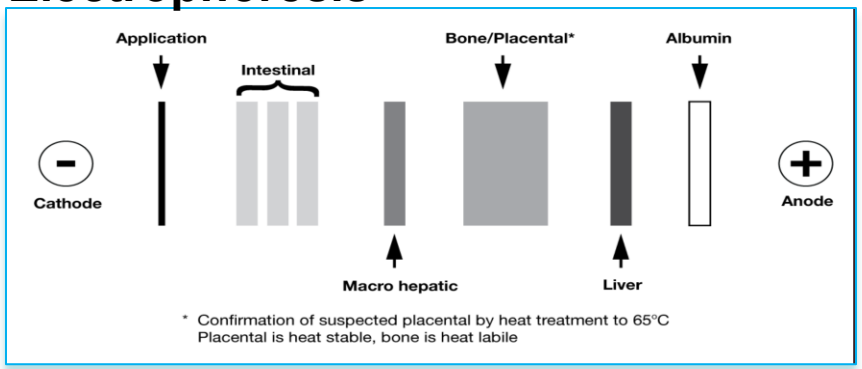
- Increase in bone fraction
  - Paget's disease of bone
  - Malignancies
    - PTHrP
    - Osteosarcomas
    - Osteoblastic mets
  - Anabolic bone agents
    - Romosozumab, PTH analogs
  - Hyperparathyroidism
  - Hyperthyroidism

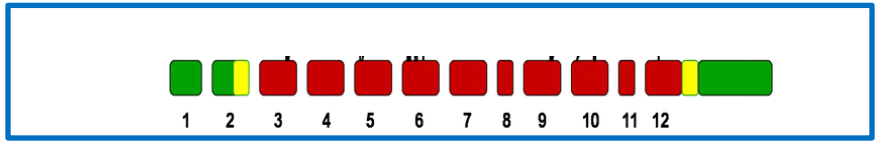
Alkaline Phosphatase Isoenzymes

- Tissue-specific isoenzymes
  - Intestinal (*ALPI* 2q37.1)
  - Placental (*ALPP* 2q37.1)
  - Germ cell (*ALPG* 2q37.1)
- Tissue Non-Specific Alk Phos = **TNAP** (*ALPL* - 1p36.1)
  - Different isoforms
  - Alternative start site
  - Differential glycosylation
    - Bone
    - Liver
    - Kidney



Electrophoresis



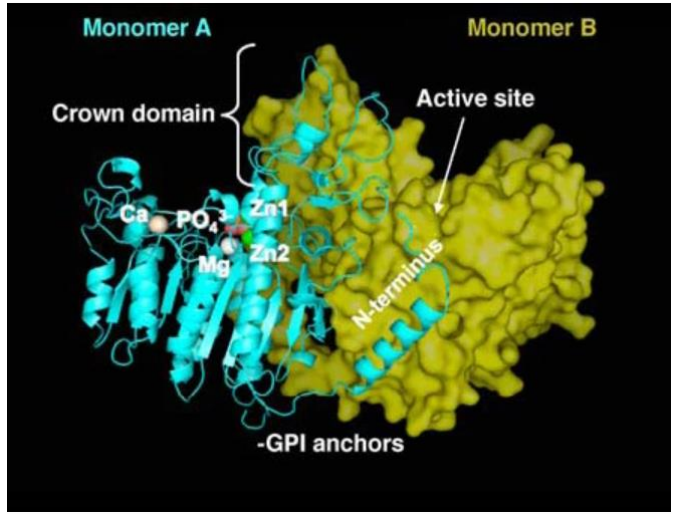


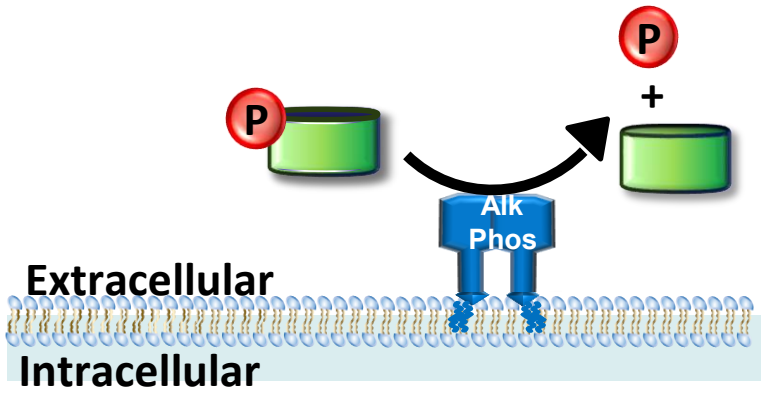
Nizet.Clin Chim Acta.2020; Makris.Calcif Tissue Int.2023; Graser.Int J Molec Sci.2021; Haahaus.Nutrients.2022

Alkaline Phosphatase

- Ectoenzymes
- GPI anchors

- Homodimers
- Require Zn+ and Mg+ as co-factors
- Many substrates

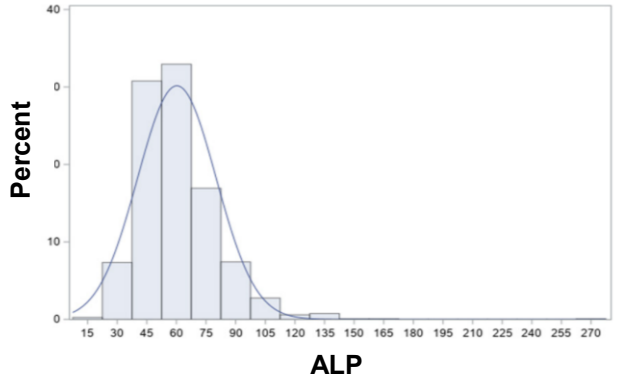




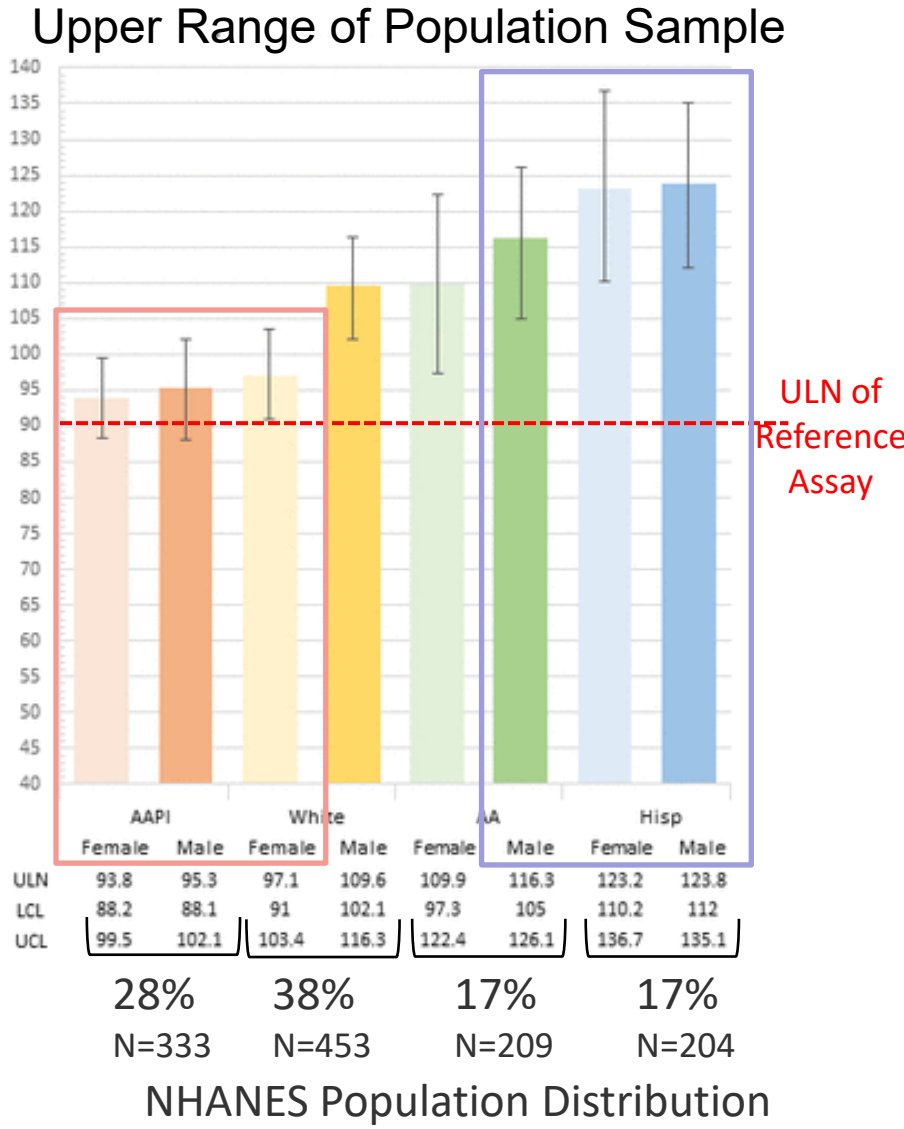
Millan.Purinergic Signaling.2006; Vimalraj.Gene.2020

Alk Phos Varies by Ethnicity & Gender

- NHANES Population Alk Phos measurement
  - N=1199 (673 F/ 526 M)
  - Mean: 60.2 IU
  - Median: 57 IU
  - Q1 47/ Q3 69

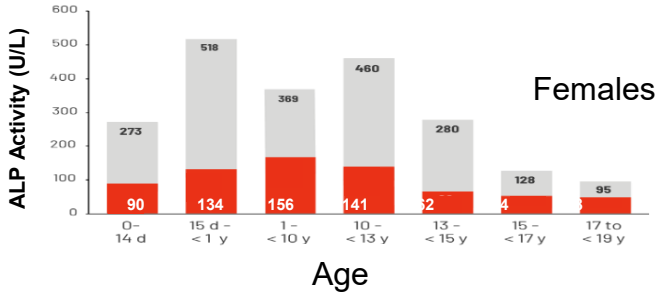


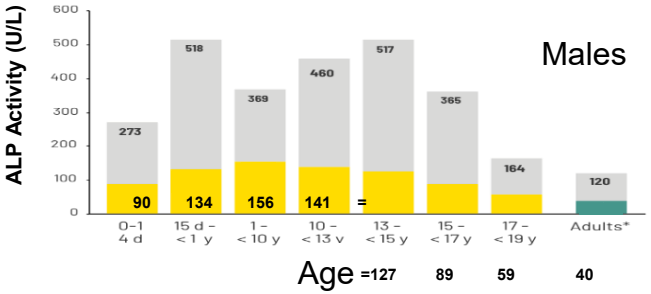
- Upper limits of normal
  - Varies by ethnicity but with significant overlap
    - Asian & White F < Hispanic & Black M
    - Trend for males > females



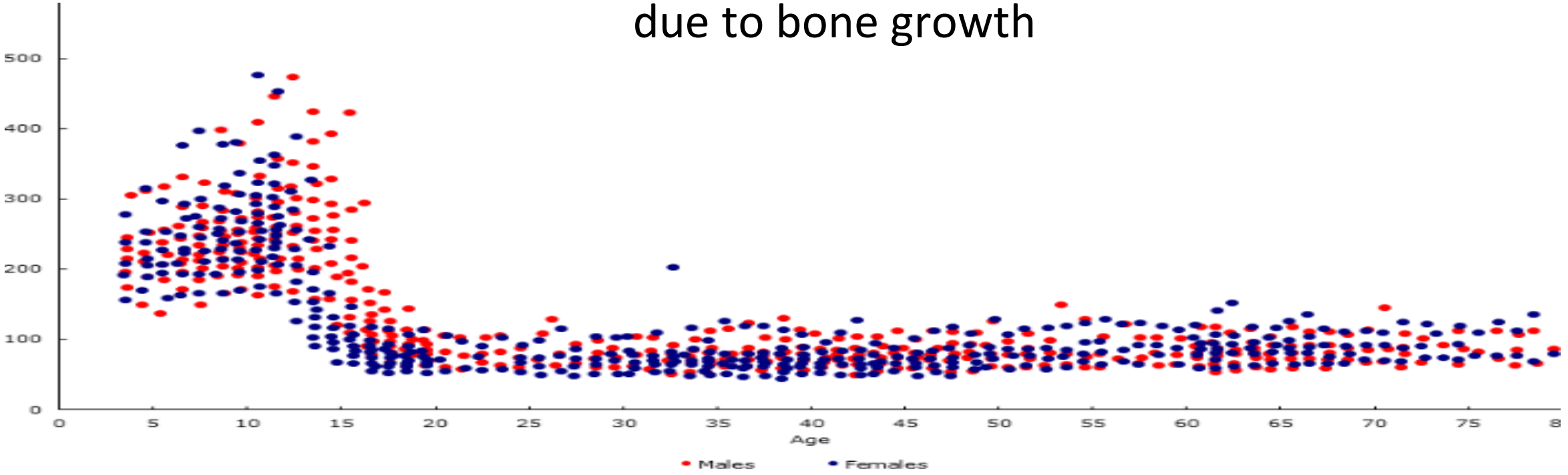
Gonzalez.BMJ Open Gastro.2020

Alk Phos Varies by Age





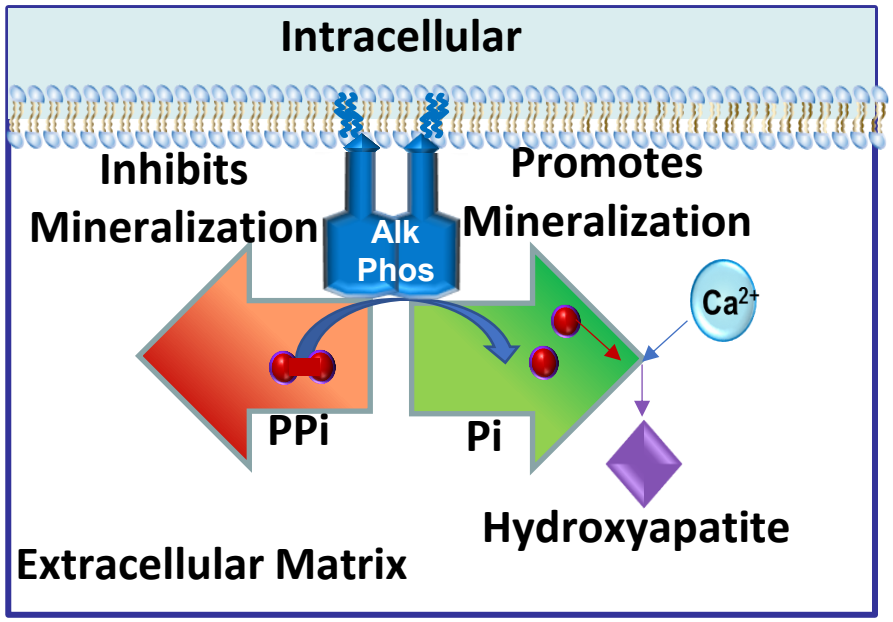
- Increased alk phos in children/young adults due to bone growth

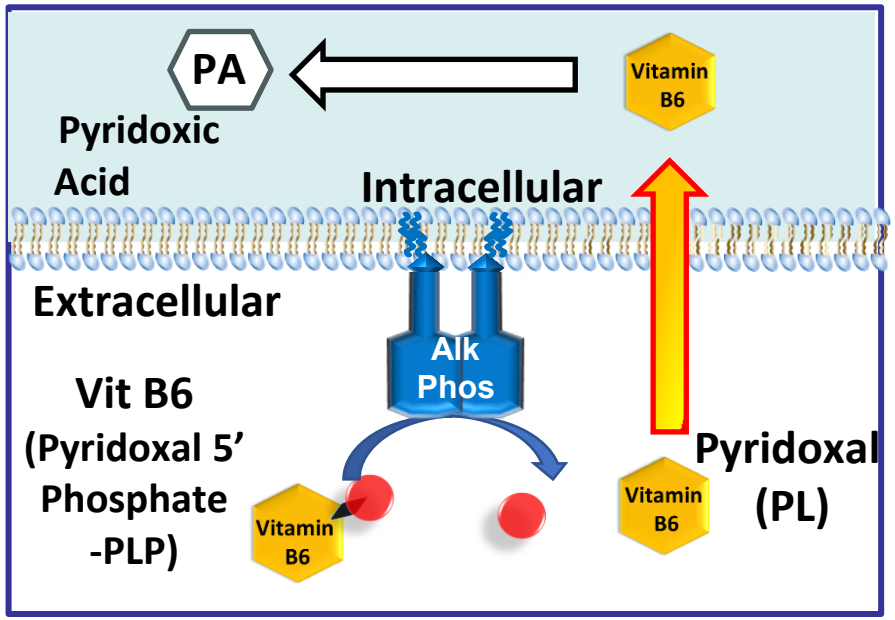


Adeli, K.Clinical Chemistry.2015

TNAP Function: Overview

- Bone
  - Promotes mineralization
    - Hydrolyzes **inhibitors** of mineralization
- Nerves
  - Vit B6 transport into cells
    - Dephosphorylate PLP to PL to cross membrane

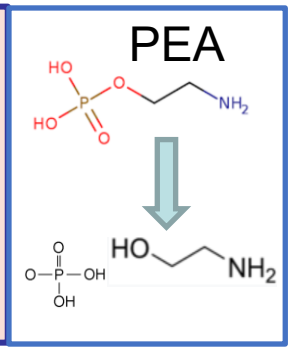




Liver (Marker)

PEA metabolism

Phosphoethanolamine to ethanolamine + Pi



Whyte.Nature Rev Endo.2017; Bianchi.Osteop Int.2020

Low Alkaline Phosphatase

Table 1. Differential Diagnosis of Hypophosphatasemia Based on the Temporal Evolution of the Low Serum ALP Value[6]

Temporal evolution of the low serum ALP value		
Persistently low	Transiently low	Precipitously low
• Hypophosphatasia (HPP: OMIM 146300,241500,241510)	• Osteogenesis imperfecta type II (OMIM 166210)	• Cardiac bypass surgery
• Cleidocranial dysplasia (OMIM166210)	• Profound hypothyroidism	• Major trauma
• Mseleni joint disease (OMIM 613342)	• Cushing's disease	• Major surgery
	• Bisphosphonate therapy	• Cancers and chemotherapy
	• Adynamic renal osteodystrophy	• Multiple myeloma
	• Milk-alkali syndrome	• Transfusion (often massive)
	• Vitamin D intoxication	• Starvation/acute caloric restriction
	• Wilson's disease	• Sepsis/multi-organ/hepatic failure
	• Nutritional deficiencies (Vit C)	• Analytic error
	• Hypomagnesemia	• Improperly collected specimen (eg, EDTA, citrate, oxalate)
	• Hypozincemia	
	• Celiac disease	
	• Pernicious anemia	
	• Radioactive heavy metal contamination	

McKiernan.JBMR.2014; Whyte.Nature Rev Endo.2017; Bianchi.Osteop Int.2020; Khan. Osteop Int.2024

Low Alkaline Phosphatase

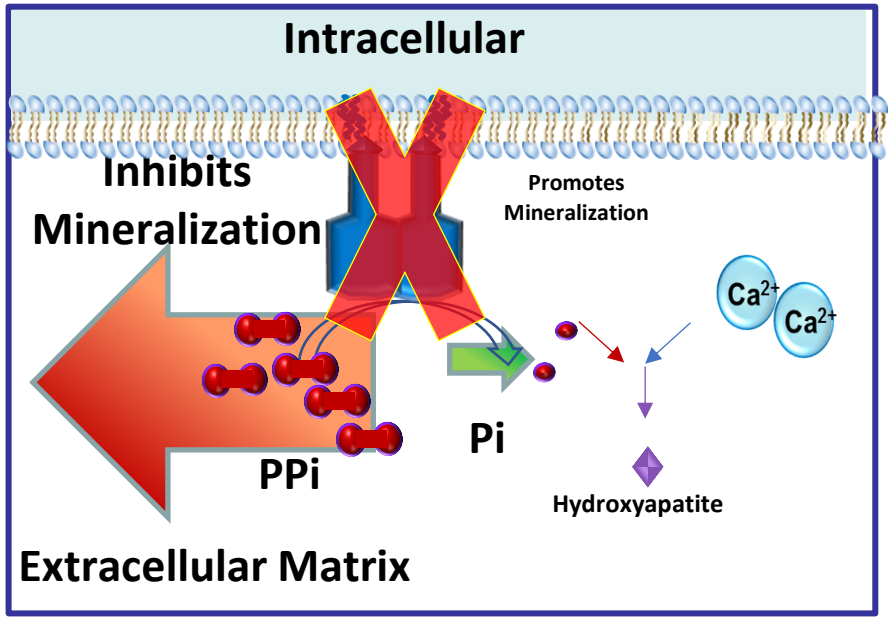
- Hypophosphatasia
- Assay Interference
  - Wilson disease (excess copper)
  - Zn^{+2} or Mg^{+2} deficiency
  - Improper collection (oxalate, citrate, EDTA)
  - Massive transfusion
  - Heavy metals
- Inappropriate reference range *(accelerated bone age)*

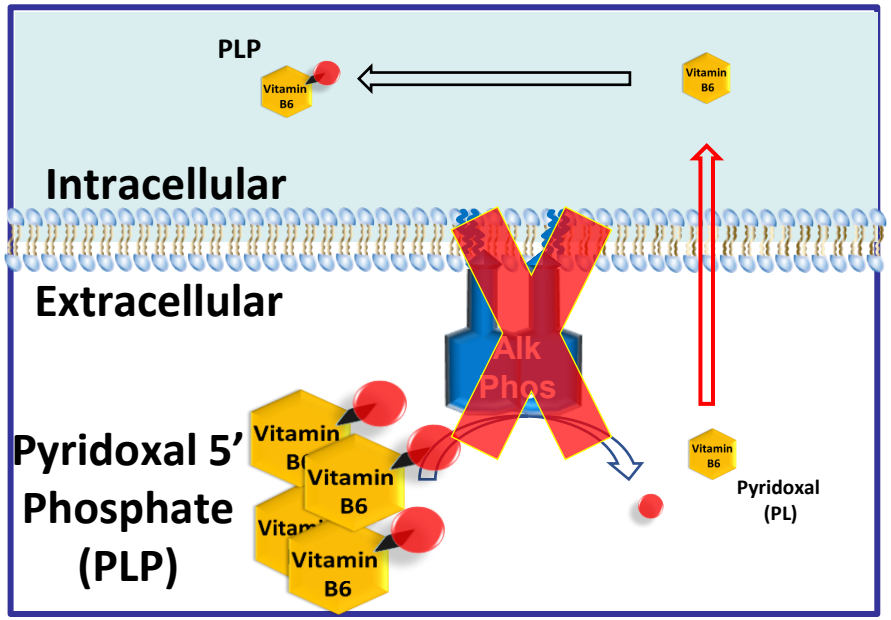
- Decreased osteoblast activity
  - Hypoparathyroidism
    - VitD intoxication, milk-alkali
  - Hypothyroidism
  - Glucocorticoid toxicity
  - Antiresorptives
    - Bisphosphonates, denosumab
    - Raloxifine, sex steroids
  - Multiple myeloma
  - Cardiac bypass/ trauma/critical illness
  - Starvation/malnutrition
    - Celiac disease
- Other
  - Pernicious/profound anemia
  - Vitamin C deficiency

Whyte.Nature Rev Endo.2017; Bianchi.Osteop Int.2020; Khan. Osteop Int.2024

Hypophosphatasia

- Pathophysiology
  - Impaired TNAP activity
  - Accumulation of substrates
    - PPi, PLP (vit B6), & PEA
- Variable clinical manifestations
  - Undermineralized bone
    - Rickets / Osteomalacia
    - Fractures
  - Chondrocalcinosis (CPPD)
  - Loose teeth
  - Seizures (respond to vitB6)
  - Hypotonia/weakness
  - MSK pain



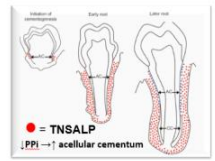


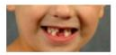
Whyte.Nature Rev Endo.2017

Clinical Subtypes

Odontohypophosphatasia

- Early loss of deciduous teeth (<5 yo)
- Weakened roots
  - ↓ Cementogenesis





Zweifler Int J Oral Sci. 2015

Perinatal Benign & Severe

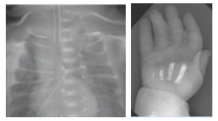
6 mo

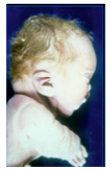
18 yr

Infantile | **Juvenile** | **Adulthood**

Perinatal

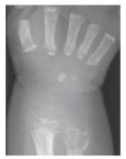
- Severe hypomineralization
  - Rachitic changes
  - Accordion limbs
  - Fractures
- Craniosynostosis
- **Hypoplastic lungs/respiratory failure**
- Vitamin B6 responsive seizure
- Stillbirth
- **Typically lethal in neonatal period**





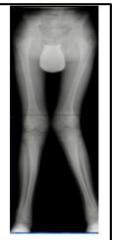
Infantile

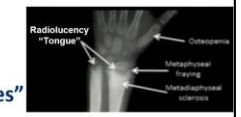
- Severe hypomineralization
  - Rachitic changes (flail chest)
  - Fractures
- **Hypercalcemia**
  - Hypercalciuria/nephrocalcinosis
- Poor growth/failure to thrive
- Hypotonia/delayed milestones
- **Vitamin B6 responsive seizure**
- **~ 50% mortality without Trx**



Childhood

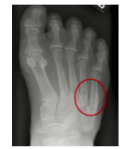
- **Variability** in clinical manifestations
- Early tooth loss w intact roots
  - Dental films w enlarged pulp chambers
- Mild- moderate hypomineralization
  - **Variable rachitic changes**
  - Fractures
  - Short stature
  - Metaphyseal lucency **"tongues"**
- Muscle weakness/waddling gait

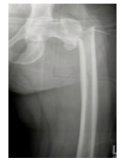




Adult

- Typically present in middle age
- Musculoskeletal complaints are most frequent presenting symptoms
- Fractures (~50% w h/o)
  - Metatarsal fractures most common
  - Subtrochanteric femoral fractures
  - Femoral pseudofractures
- Dental disease
  - May have h/o early tooth loss
- Ca-Pyrophosphate deposition





Whyte.Nature Rev Endo.2017; Bianchi.Osteop Int.2020

Clinical Subtypes

1:300K
Autosomal Recessive

1:7K -1:175
Autosomal Dominant

Perinatal | 6 mo | 18 yr

Infantile | **Juvenile** | **Adulthood**

Perinatal

- Severe hypomineralization
  - Rachitic changes
  - Accordion limbs
  - Fractures
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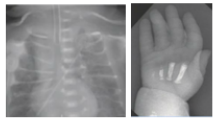

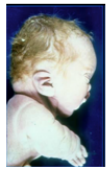

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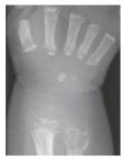

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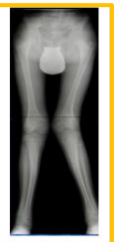
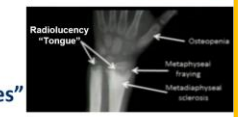
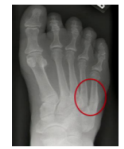


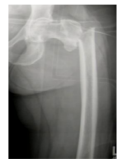


Variable Severity

Adult

- Typically present in middle age
- Musculoskeletal complaints are most frequent presenting symptoms
- Fractures (~50% w h/o)
  - Metatarsal fractures most common
  - Subtrochanteric femoral fractures
  - Femoral pseudofractures
- Dental disease
  - May have h/o early tooth loss
- Ca-Pyrophosphate deposition





Whyte.Nature Rev Endo.2017; Bianchi.Osteop Int.2020

Adult Patients with HPP

1:300K
Autosomal Recessive

1:7K -1:175
Autosomal Dominant

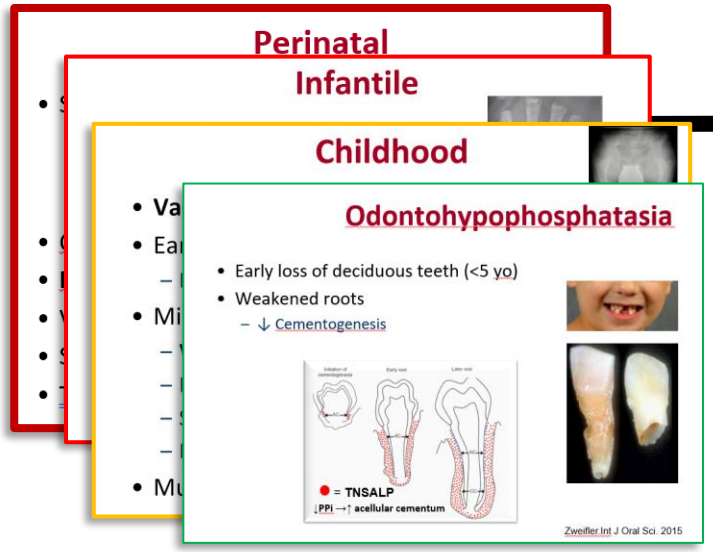
Prevalence

Severity

Perinatal **Infantile** **Juvenile**

18 yr

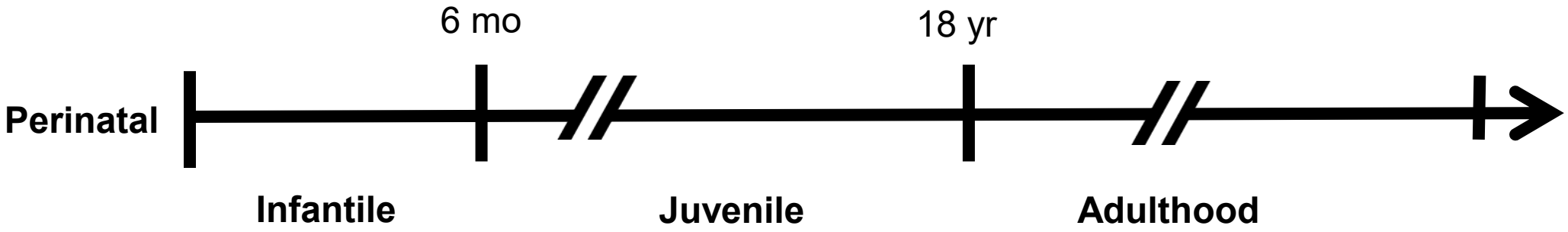
Adulthood

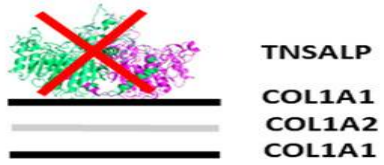
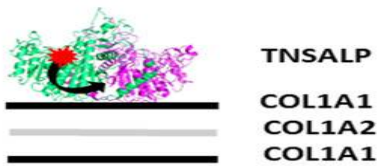
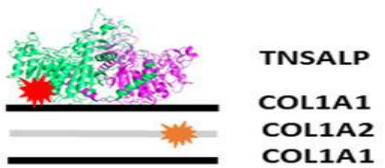
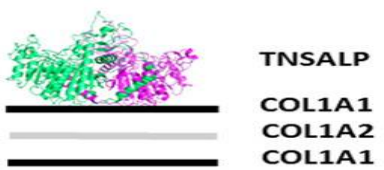


- Childhood onset with continuous symptoms
- Childhood onset ->quiescence-> symptoms in adulthood

- Adult onset
  - ERT not FDA approved
- Asymptomatic silent “carriers”

Genetics Based Nosology- ALPL



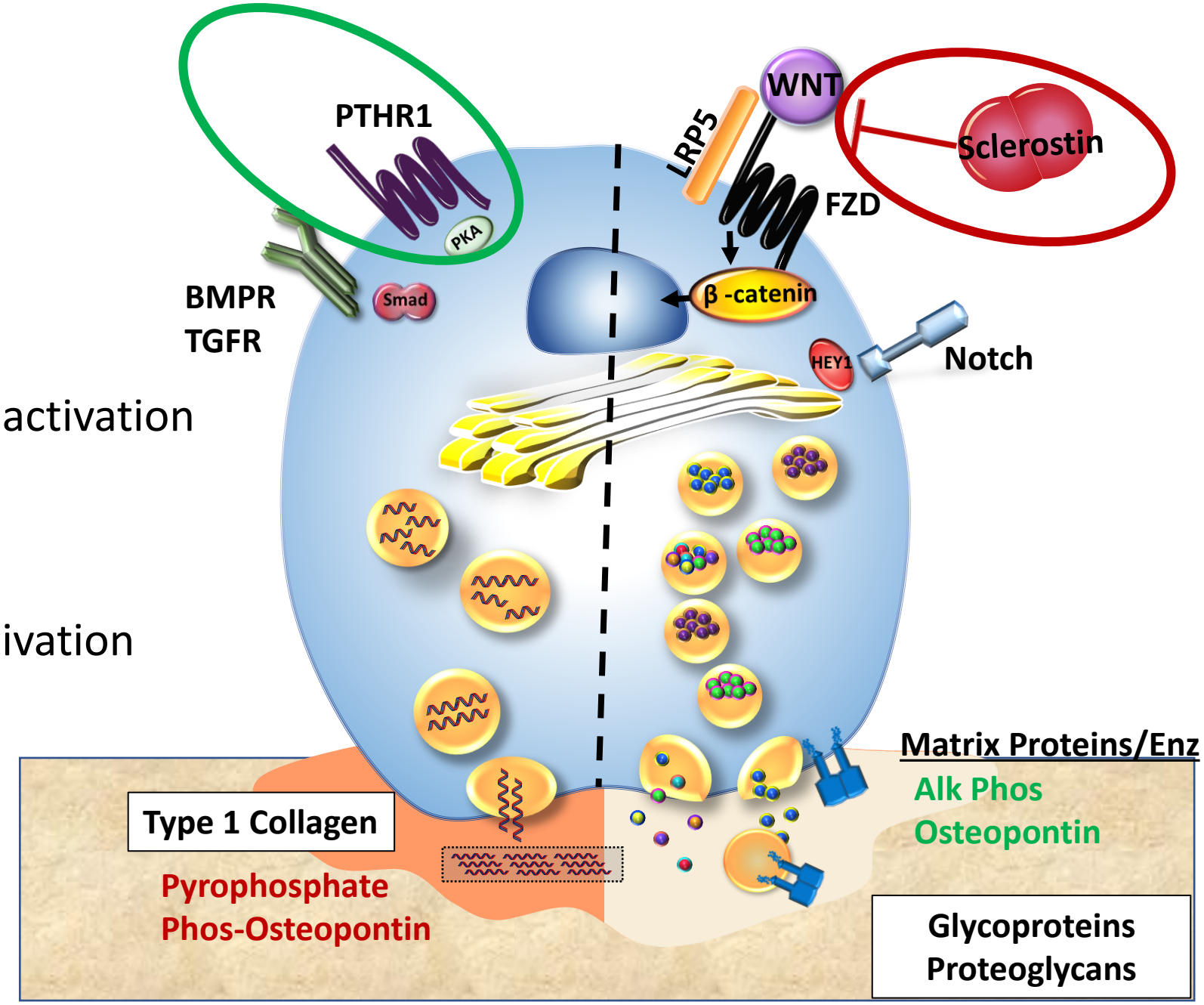
HPP subtype	Severe	Moderate	Mild	Wild-type
Inheritance	AR	AR or AD_{DNE}	$AD_{haploinsuff}$	-
Prevalence	1/300,000	1/2430	1/508	-
Actual classification	Perinatal, infantile	Infantile, childhood, odonto, adult (typical)	Adult (unspecific signs)	-
Genotypes	s/s, Sd/S, Sd/Sd, m/m_{homoz}	Sd/m, s/m, Sd/N	s/N, m/N	N/N
				

Mornet.Eur J Hum Genet.2021; https://alplmutationdatabase.jku.at/portal (curated by Wolfgang Högler)

Clinical Manifestations

- **Skeletal**
  - Rickets/osteomalacia
  - Craniosynostosis
  - Non-healing fractures
  - Chronic bone pain
- **Renal**
  - Nephrocalcinosis
  - Kidney stones
- **Rheumatologic**
  - Chondrocalcinosis
  - Progressive arthritis
- **Dental**
  - Early tooth loss
- **Neurologic**
  - Seizures
  - Neuropathy
  - Anxiety/ depression
  - Chronic fatigue
  - Pain*
- **Muscular**
  - Myopathy
  - Myalgias
  - Weakness
  - Impaired ambulation

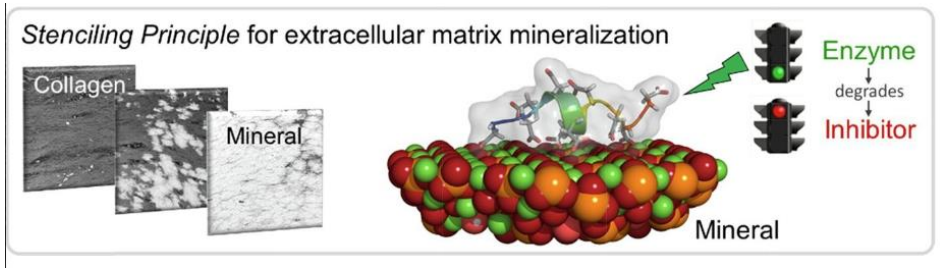
- **PTH Receptor**
  - Stimulates osteoblast activation
- **Sclerostin**
  - Inhibits osteoblast activation

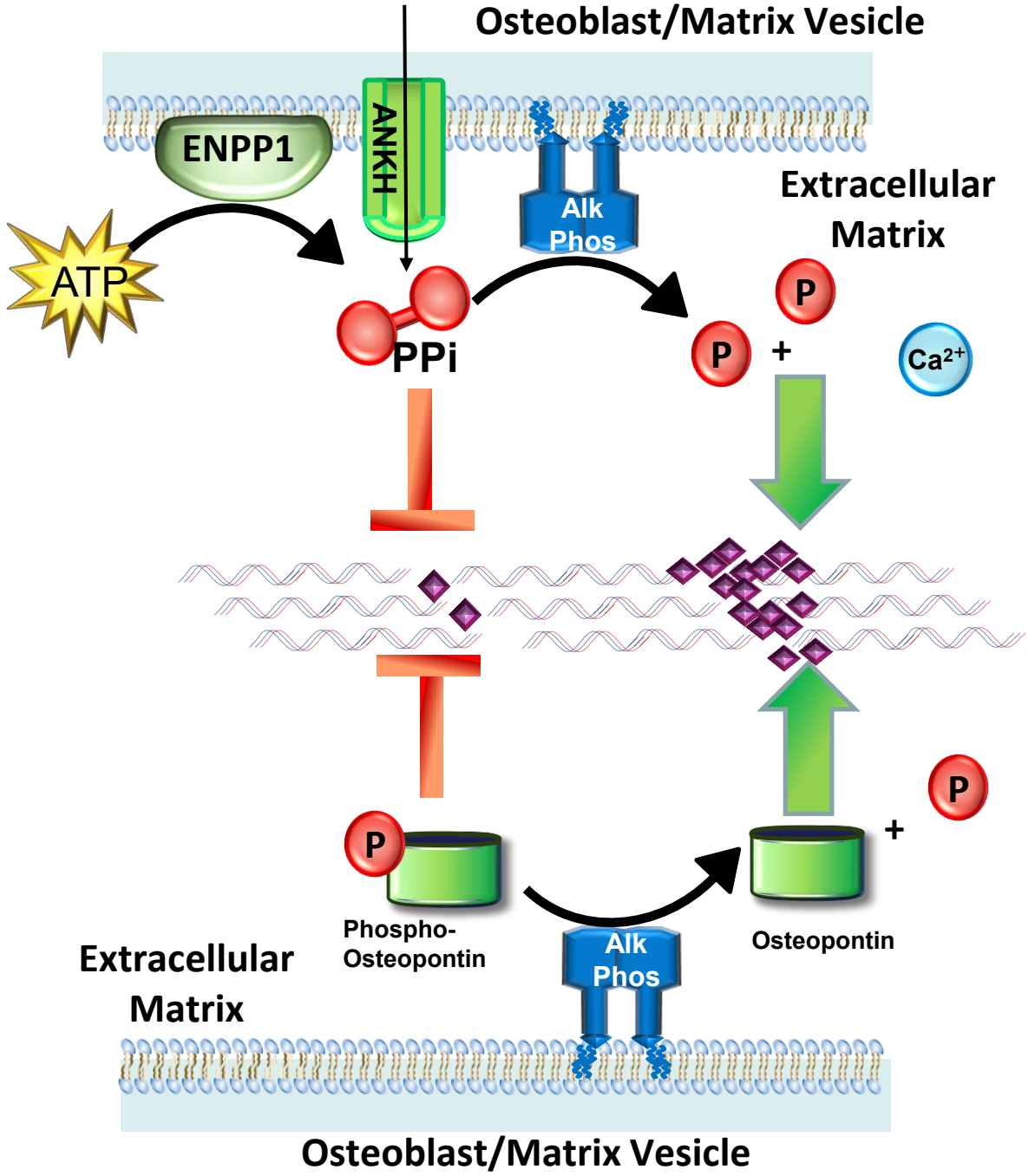


Whyte.Endocrinology.2015

Bone Mineralization

- Mineralization inhibitors
  - Pyrophosphate (PPi)
    - Hydroxyapatite formation is favored when Pi:PPi ratio (>100)
  - Phospho-Osteopontin
- Alk phos inactivates the inhibitors

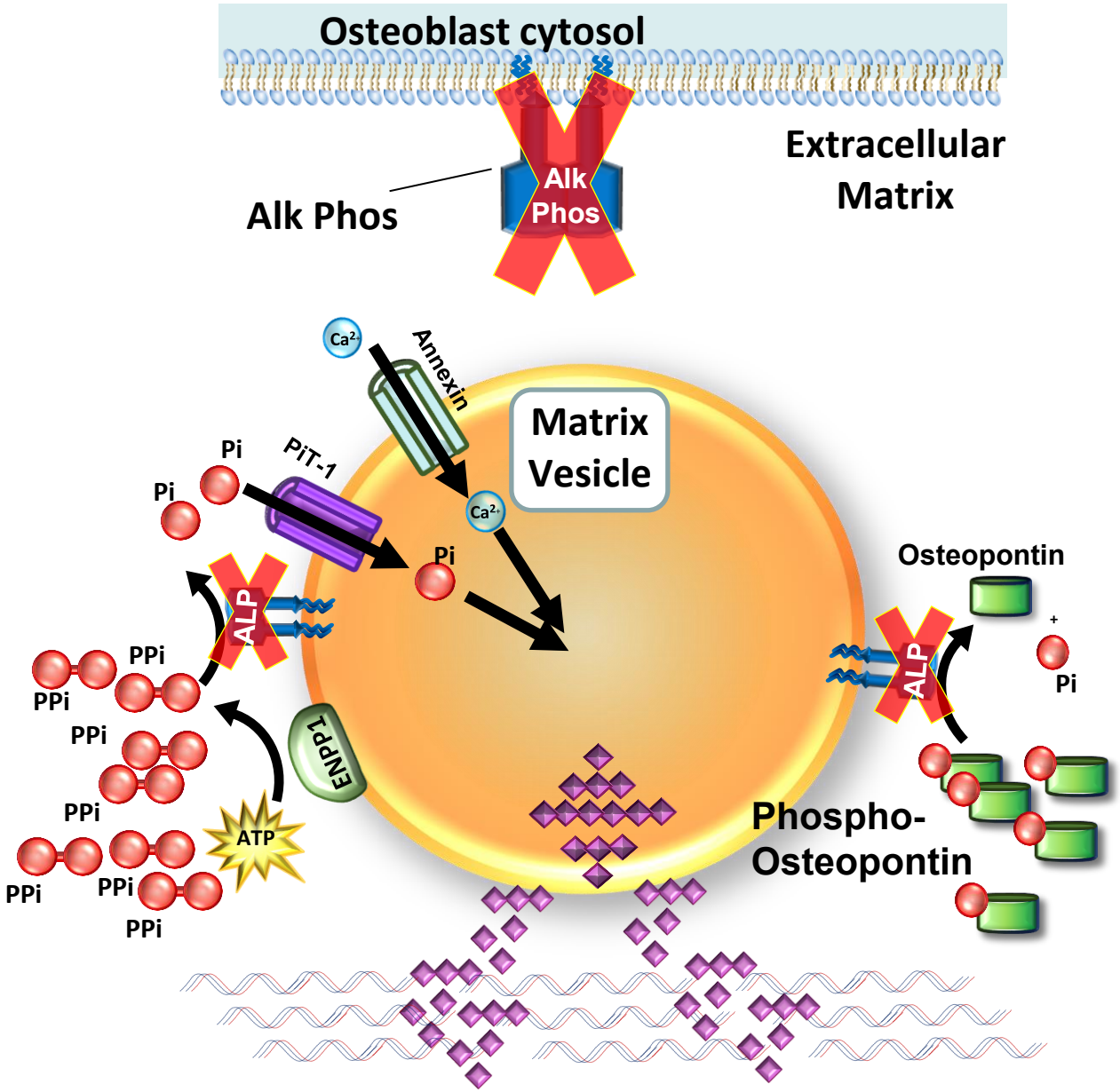




Liedtke.Biomolecules.2020

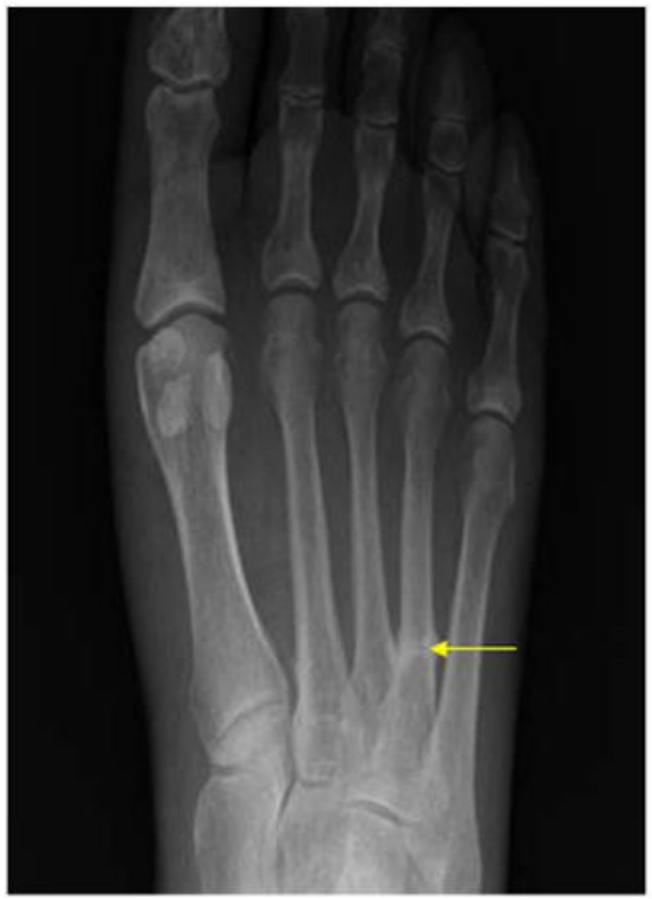
Hypophosphatasia

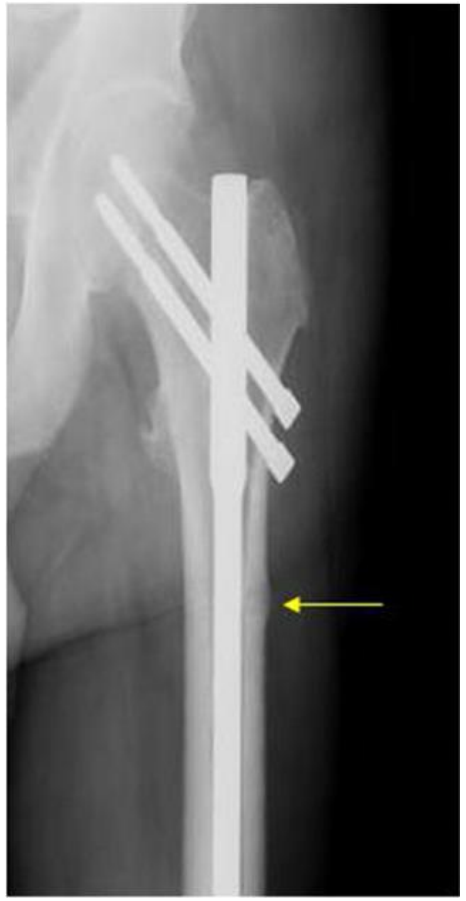
- Impaired alk phos activity allows accumulation of mineralization inhibitors
  - Pyrophosphate
  - Phospho- Osteopontin
- High PPi and P-Ospn block propagation of hydroxyapatite crystals
- Results in demineralized bone



Liedtke.Biomolecules.2020

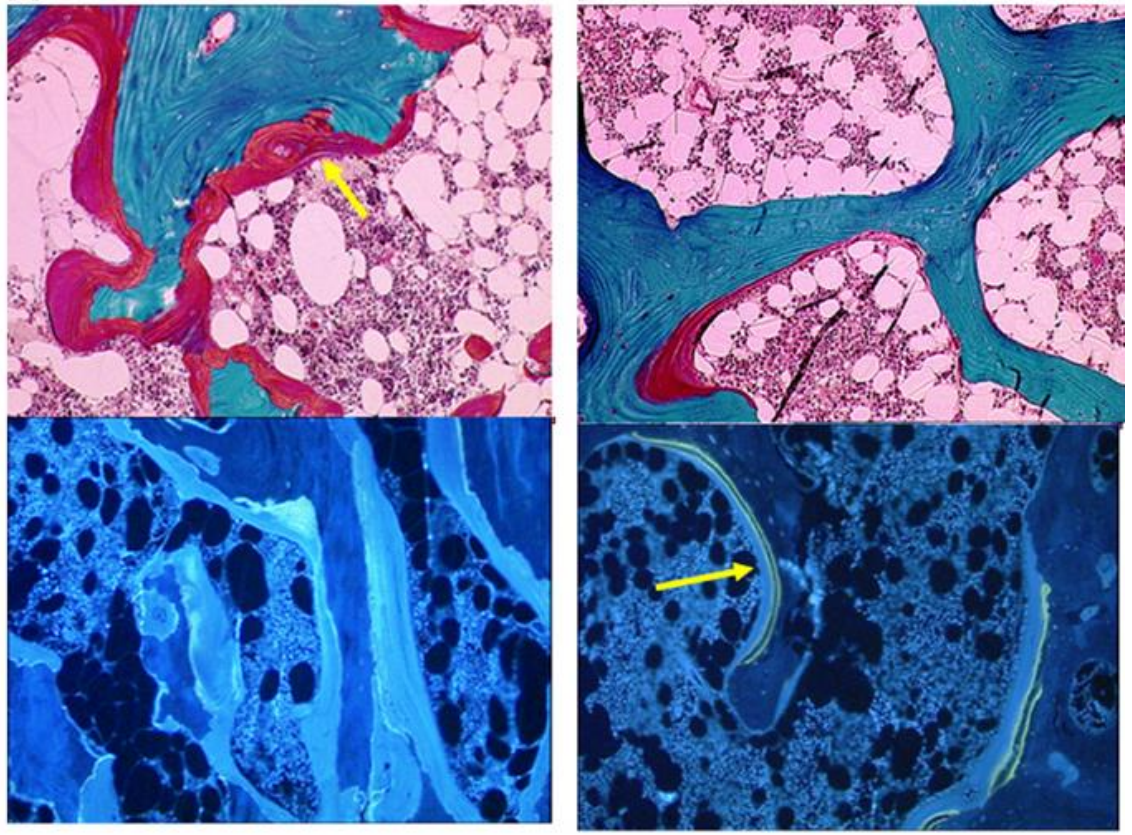
Adults with HPP Have Variable Mineralization Defects





Osteomalacia /
Low bone turnover

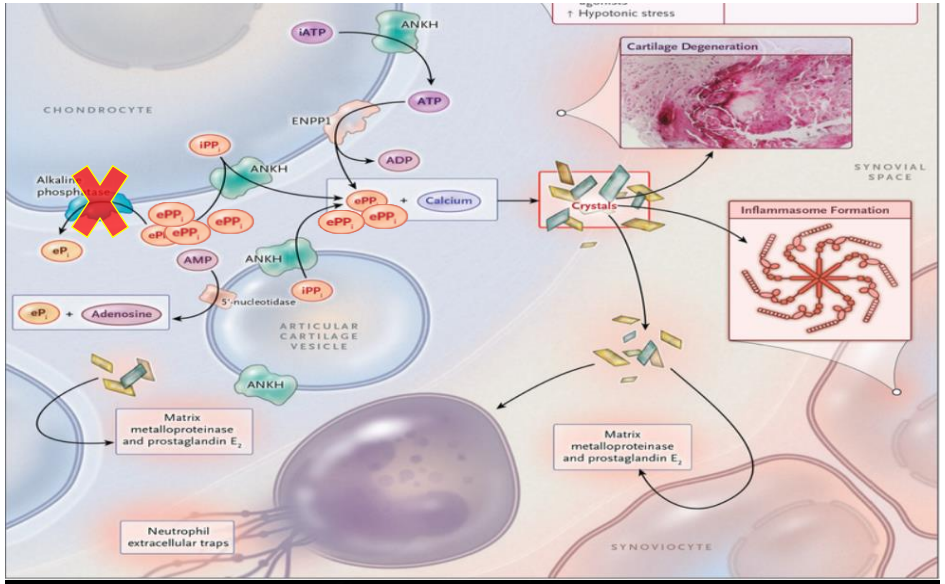
Normal mineralization &
bone turnover

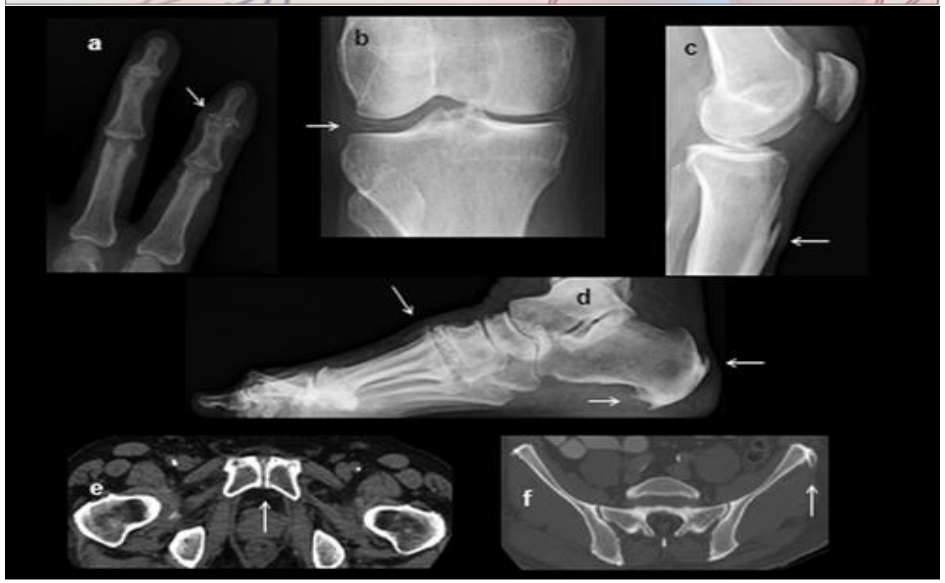


Berksethetal.Bone.2013

Extra-Skeletal Calcification

- Biochemical abnormalities
  - Hypercalciuria
  - Hypercalcemia
  - Hyperphosphatemia
  - High pyrophosphate
- Ectopic calcification
  - Renal
    - Kidney stones/nephrocalcinosis
  - Rheumatologic
    - Calcium Pyrophosphate Deposition Dz
      - Favored when Pi:Ppi <3
    - Enthesopathy





McKiernan.JBMR.2014, Rosenthal.NEJM.2016

Diagnosis of Hypophosphatasia

- **Major Criteria**
  - *ALPL* gene variant
  - ↑ Natural substrates
    - Vit B6 (PLP)
    - Urine PEA
    - (PPi*) *- not clinically available
  - Atypical femur fractures
  - Recurrent metatarsal stress frxs
- **Minor Criteria**
  - Poorly healing fractures
  - Chronic musculoskeletal pain
  - Early atraumatic loss of teeth
  - Chondrocalcinosis
  - Nephrocalcinosis

In adults w persistently low alk ϕ:

- **2 Major Criteria**

  OR

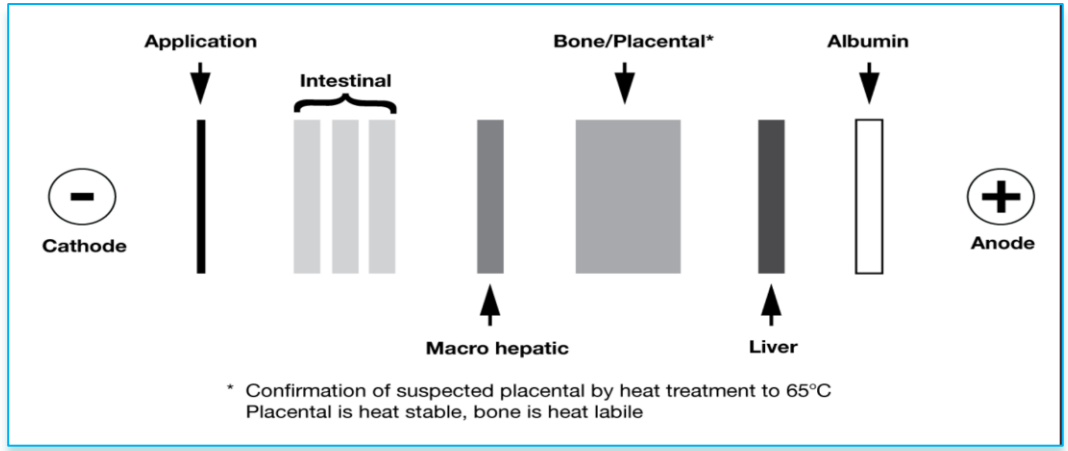
- **1 Major +2 Minor**

Khan.Osteoporos Int.2024; Brandi.Osteoporos Int.2024

Fractionated Alkaline Phosphatase

- Alkaline Phosphatase
  - **22 (21-25) [35-104 U/L]**
- Fractionated Alk Phos
  - TNSALP- 13.9 U/L [28.3-118.7], 63% [>80%]
    - Liver 1 - **3.7 U/L [16.2-70.2], 17% [27.8-76.3%]**
    - Liver 2 - 0.5 U/L [0-5.8], 2% [0-8%]
    - Bone - **9.7 U/L [12.1-42.7]**, 44% [19.1-67.7%]
  - Tissues Specific alk phos
    - Intestinal- 8.1 U/L [0-11], **37% [0-20.6%]**
    - Placenta - 0
- Bone specific Alk Phos
  - **3.5 ug/L [7.0 -22.4]**

↓ Liver and Bone Aϕ (TNSALP)
Normal Intestinal Aϕ - higher percentage of total



Electrophoresis

Komaru.The FEBS Journal.2019; Sharma.Ind J Clin Biochem.2014; Graser.Int J Molec Sci.2021

Diagnosis of Hypophosphatasia

- **Major Criteria**
  - *ALPL* gene variant
    - **Heterozygous pathogenic nonsense p.Tyr101***
  - ↑ Natural substrates
    - Vit B6 (PLP)
      - **↑Vit B6 (PLP) 109-227** [5-50 µg/L]
    - Urine PEA
      - **↑ Urine PEA 65-98** [<48 nmol/mg Creat]
    - (PPi*) *- not clinically available
  - Atypical femur fractures
  - Recurrent metatarsal stress frxs
    - **2 metatarsal fractures**
- **Minor Criteria**
  - Poorly healing fractures
    - **Recurrent fractures after ORIF**
  - Chronic musculoskeletal pain
    - **Fibromyalgia**
  - Early atraumatic loss of teeth
    - **Lost primary teeth @4 yo**
  - Chondrocalcinosis
    - **CaPyrophosphate crystal deposition in hands & knees**
  - Nephrocalcinosis
    - Normal renal U/S

In adults w persistently low alk ϕ:

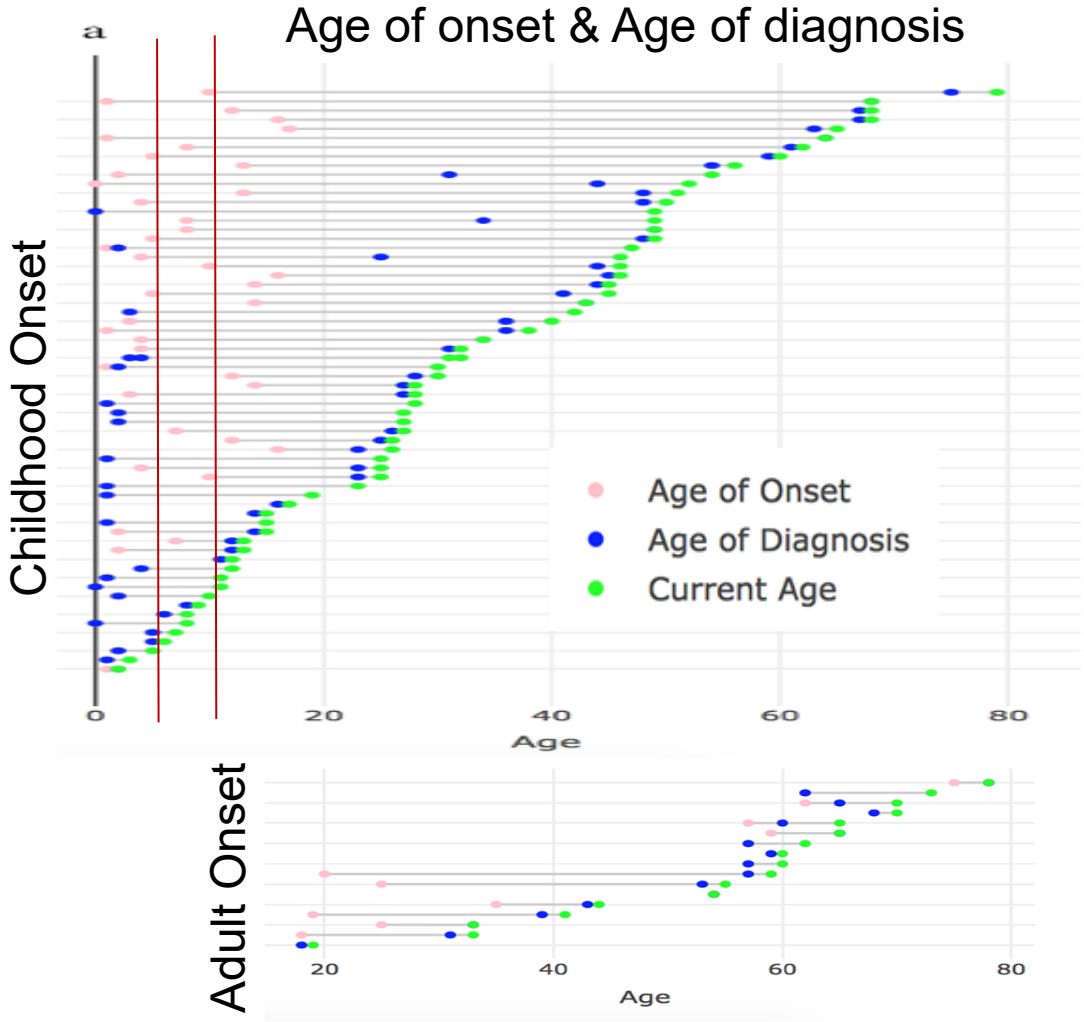
- **2 Major Criteria** √

  OR
- **1 Major +2 Minor** √

Khan.Osteoporos Int.2024; Brandi.Osteoporos Int.2024

Diagnosis Is Frequently Delayed

- Dx of HPP was frequently delayed
  - If symptom onset <5 yo, likely diagnosed in childhood
  - If symptom onset after 10, likely not diagnosed in childhood
- Skeletal symptoms appeared earlier & recognized earlier
  - First HPP manifestation
    - 12.3 yo w skeletal symptoms
    - 22.1 yo w muscular/pain symptoms



Colazo.OI.2019; Dahir.Front Endocrinol.2023

Treatment (Mineralization)

- Avoid
  - Excess Ca, vitD, Phos
    - Nephrocalcinosis
    - Ectopic calcifications
  - **Antiresorptives**
    - **Case series with ↑ AFF**

↓ Alk Phos

- Anabolics
  - Teriparatide/Abaloparatide
  - Romosozumab
- Enzyme replacement tx
  - Asfotase alfa

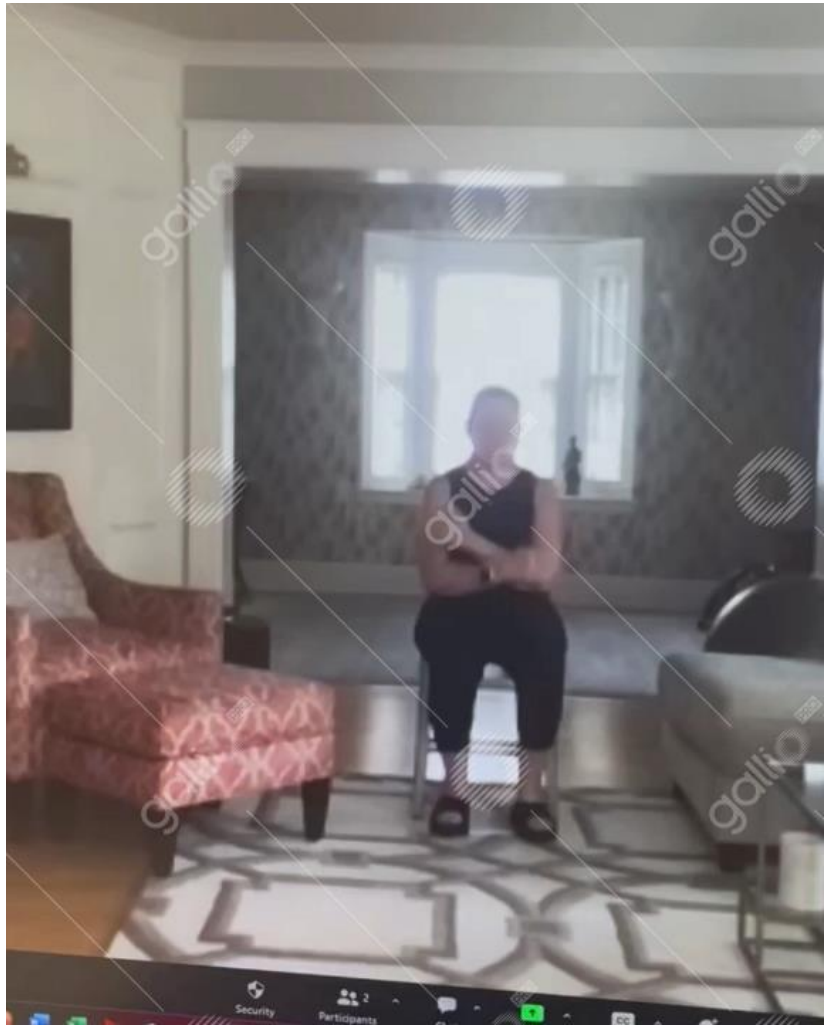
↑ Alk Phos

Sutton.JBMR.2012; Whyte.JCEM.2007; Shapiro.JBMR.2017; Rolvien.Bone.2019.

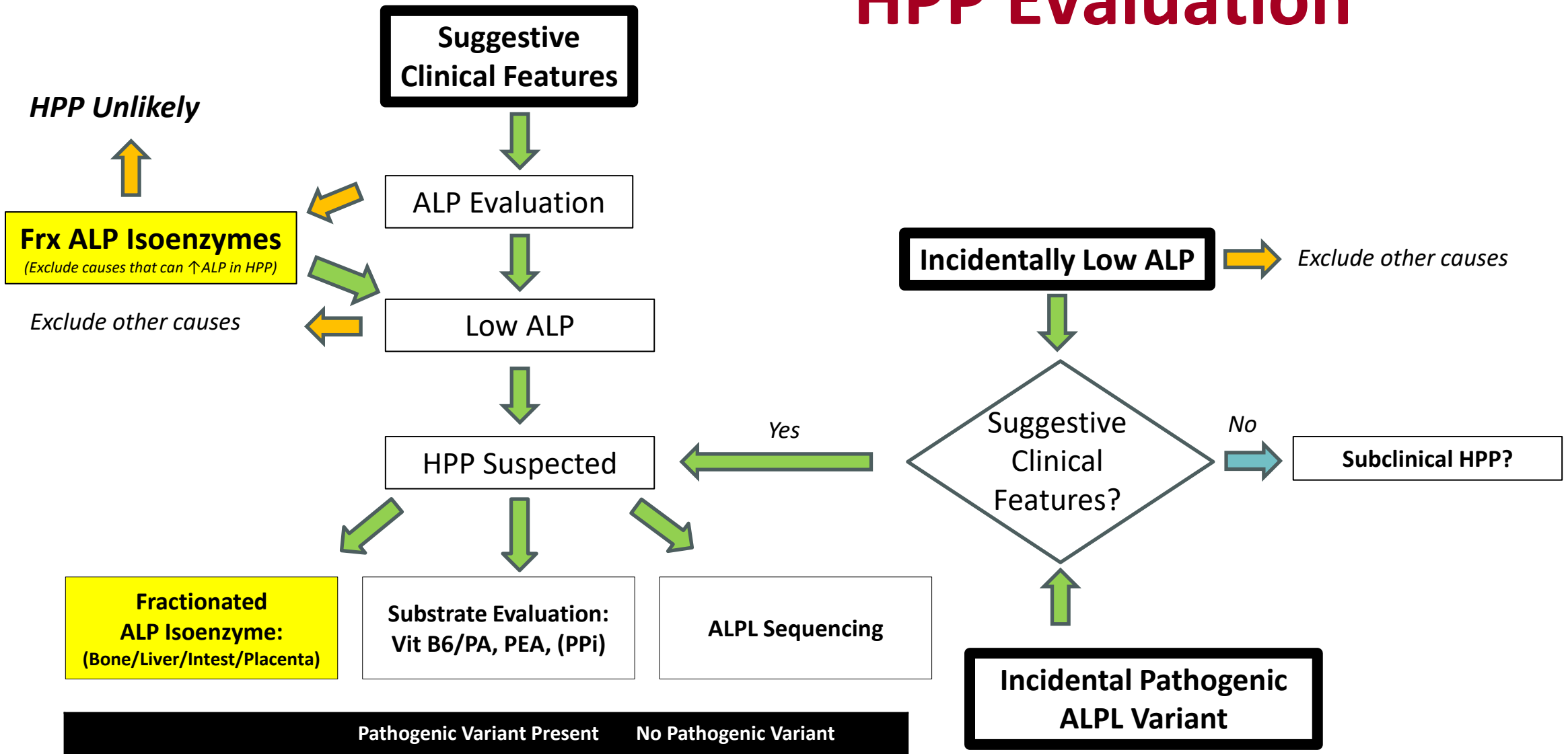
Repeated Chair-Rise Test (Video)

27.5 seconds

12.5 seconds



HPP Evaluation



	Pathogenic Variant Present	No Pathogenic Variant
Abnormal Substrates/Liver Isoform	**Definite HPP**	**Likely HPP**
Normal Substrates/Liver Isoform	**Likely HPP**	**HPP Uncertain/ Other**