

# A Missed Diagnosis

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- **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

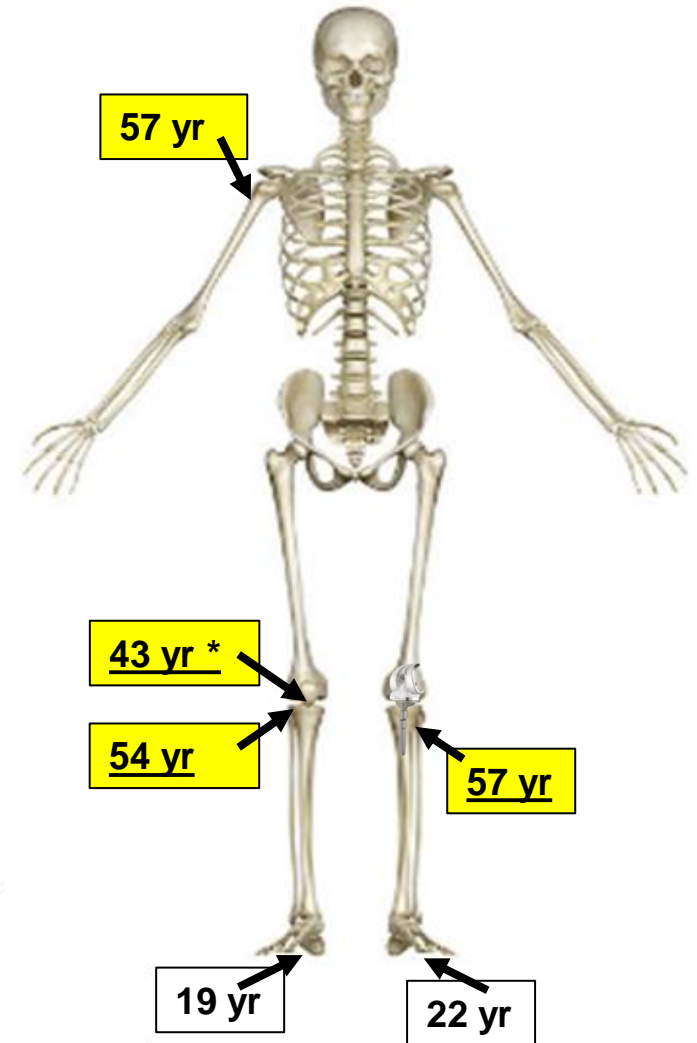
# Referral

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 illicit
  - 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 Cushingoid
- **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

# Osteoporosis Classification

- Osteoporosis

- T score  $\leq -2.5$

- Or presence of fragility fracture

 **TREAT!**

- Osteopenia

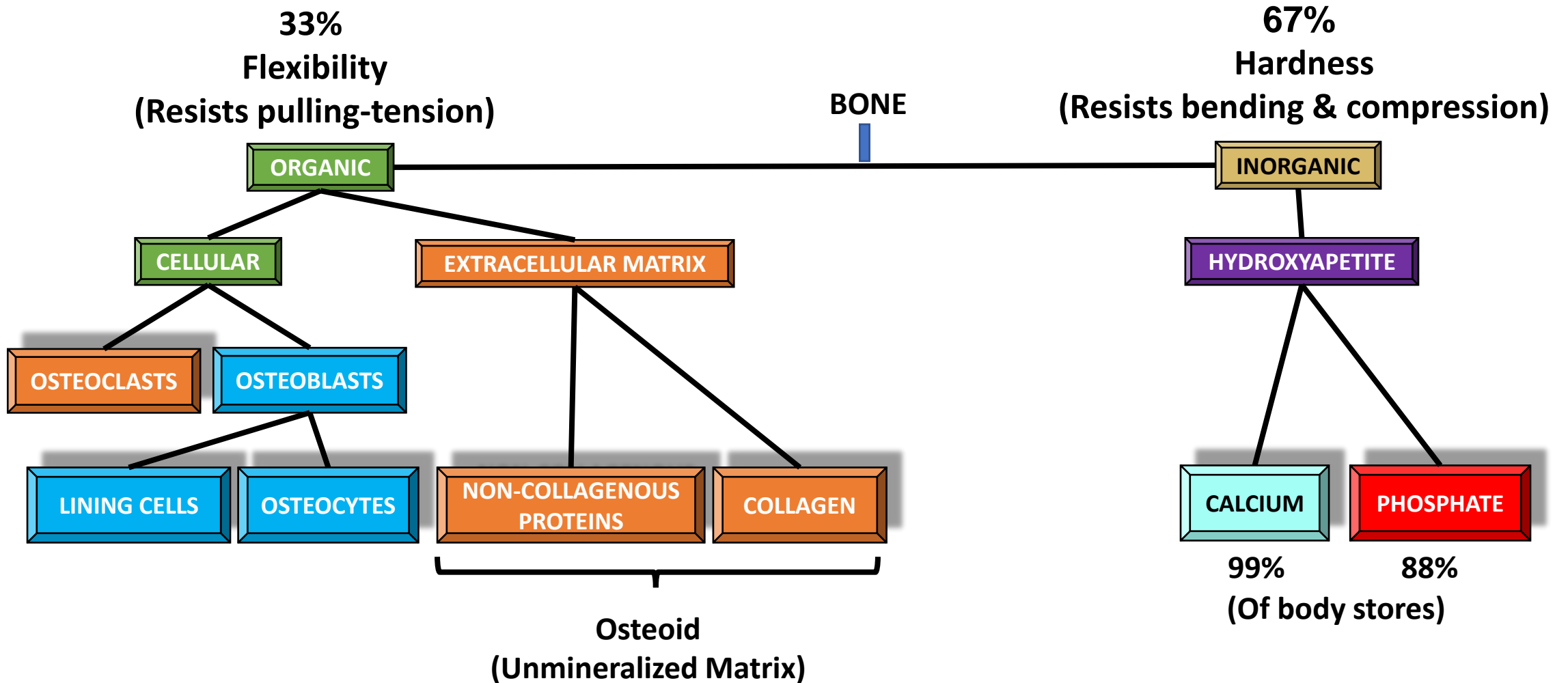
- T score: -1 to -2.5

 **Treat?**

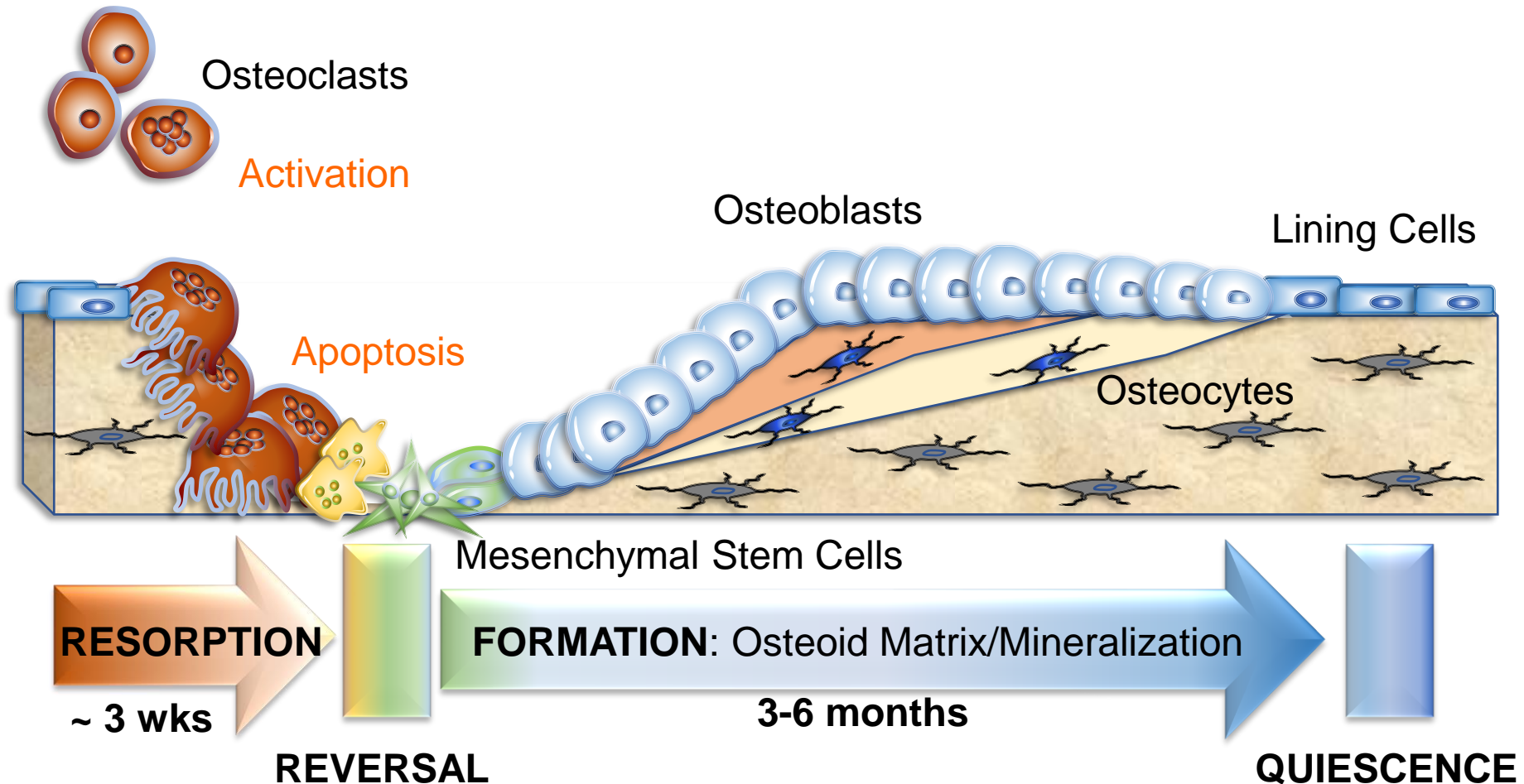
**FRAX Calculator**

**10 yr MOP  $\geq 20\%$ , hip frx  $\geq 3\%$**

# Bone Composition

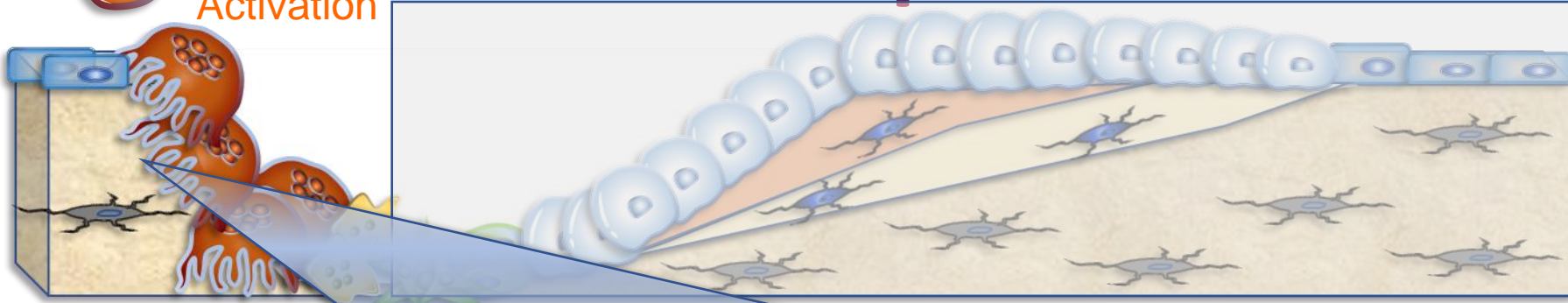


# Normal Bone Remodeling

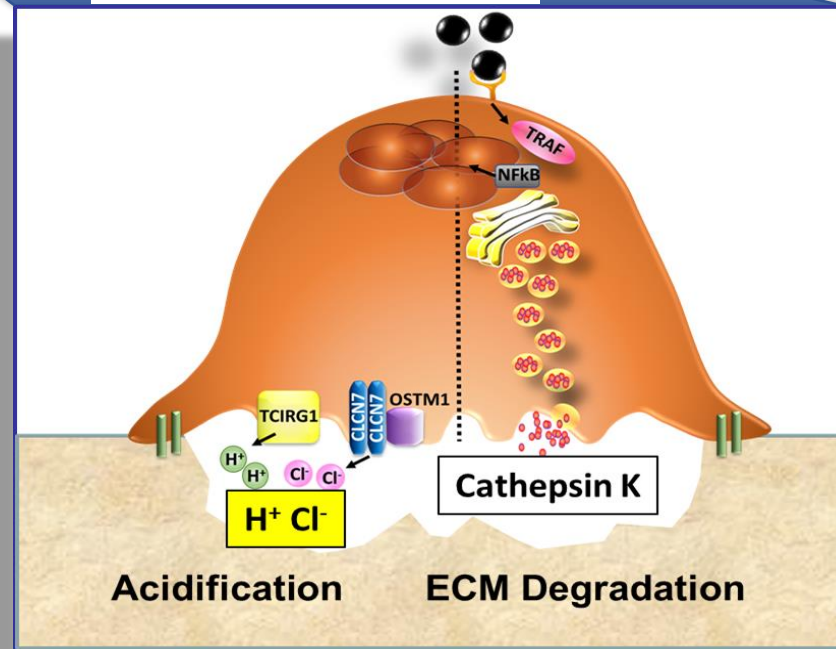
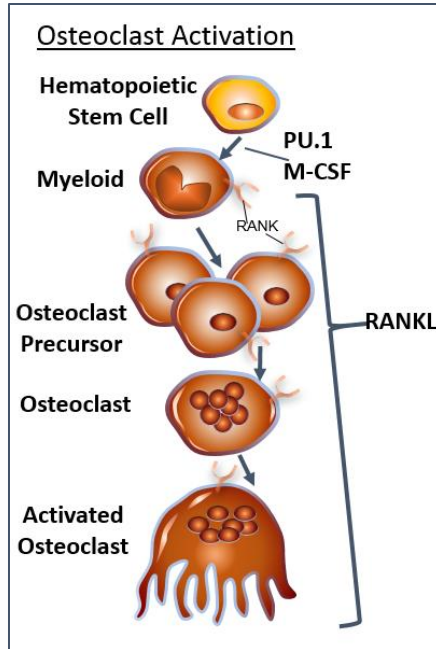




# Bone Resorption

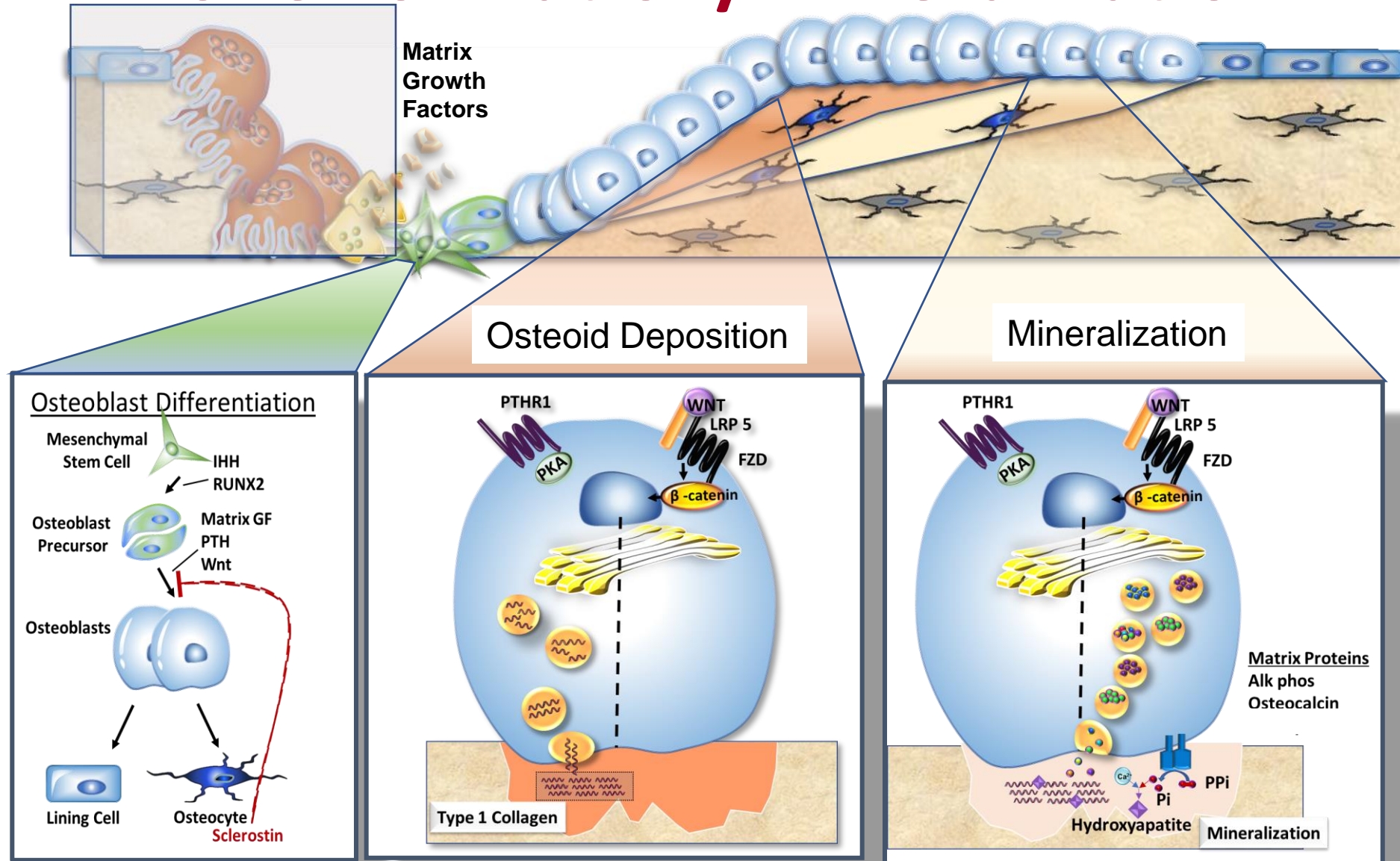


## Matrix Degradation





# Bone Formation/Mineralization



# Bone Pathology

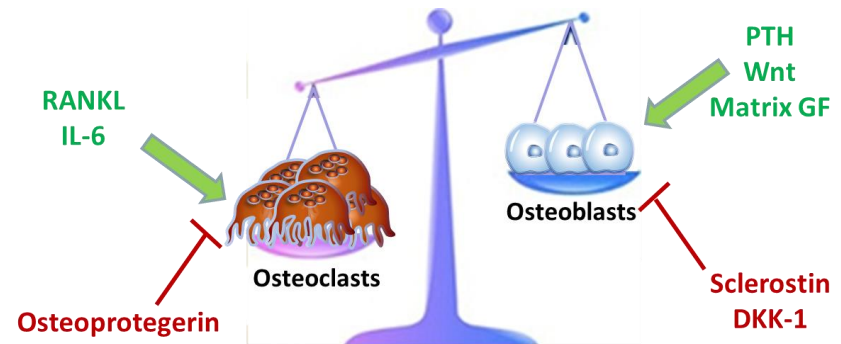
Multiple fractures

## Osteoporosis/Osteopenia

Resorption > Formation



Normal Bone





# Secondary Causes of Osteoporosis

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

# Treatment

## Anti-Resorptives

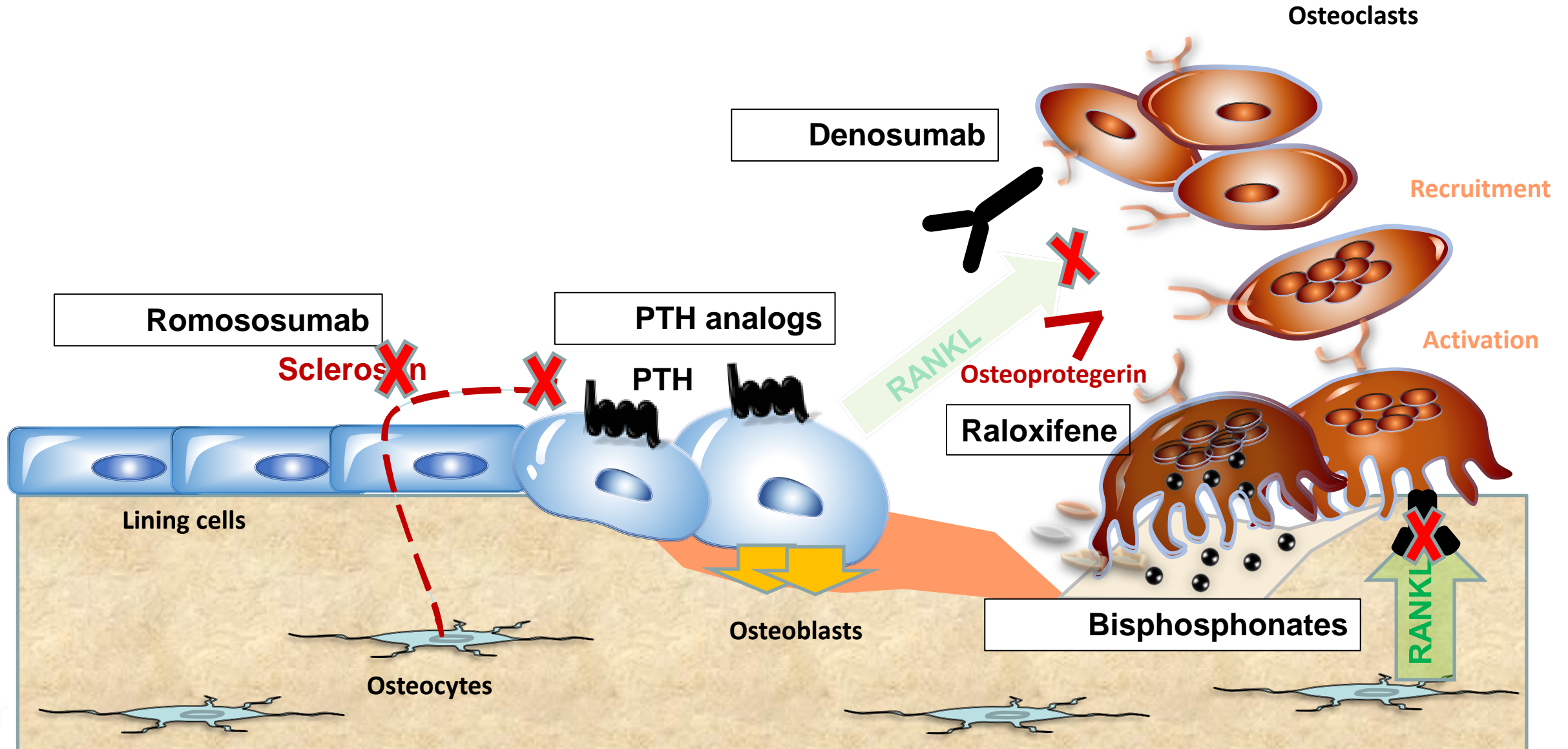
- Bisphosphonates
  - Alendronate (Fosamax)
  - Risedronate (Actonel)
  - Zoledronate (Reclast)
  - Ibandronate (Boniva)
- Denosumab (Prolia)

## Anabolics

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

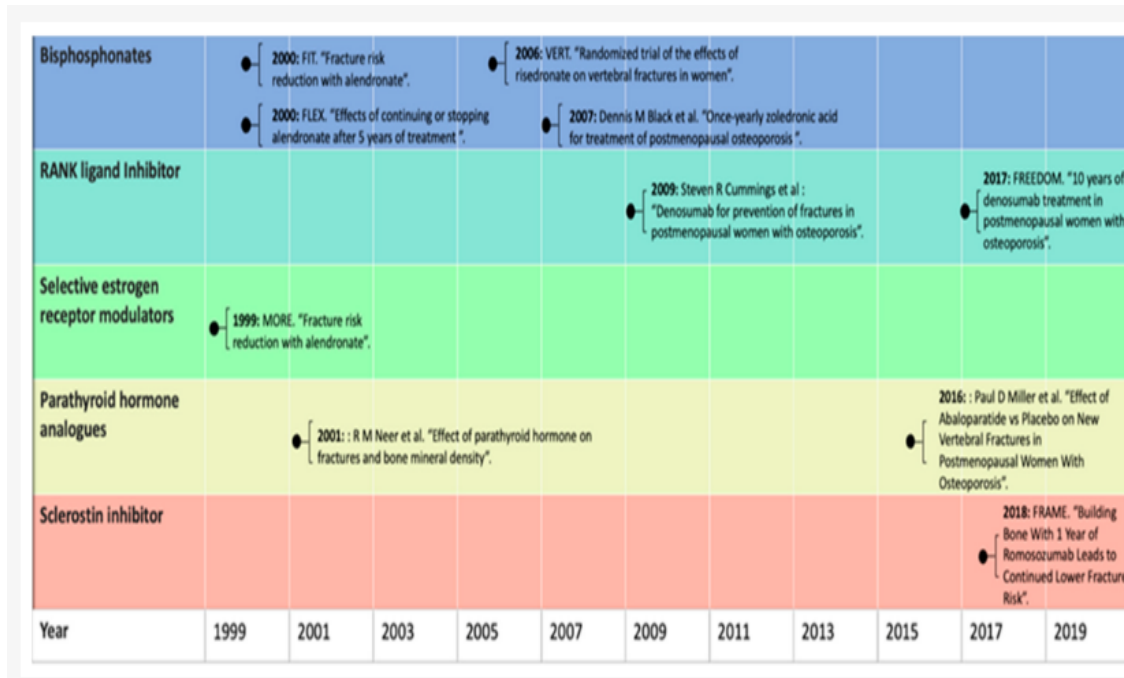
**How do they work?**

# Mechanism of Action

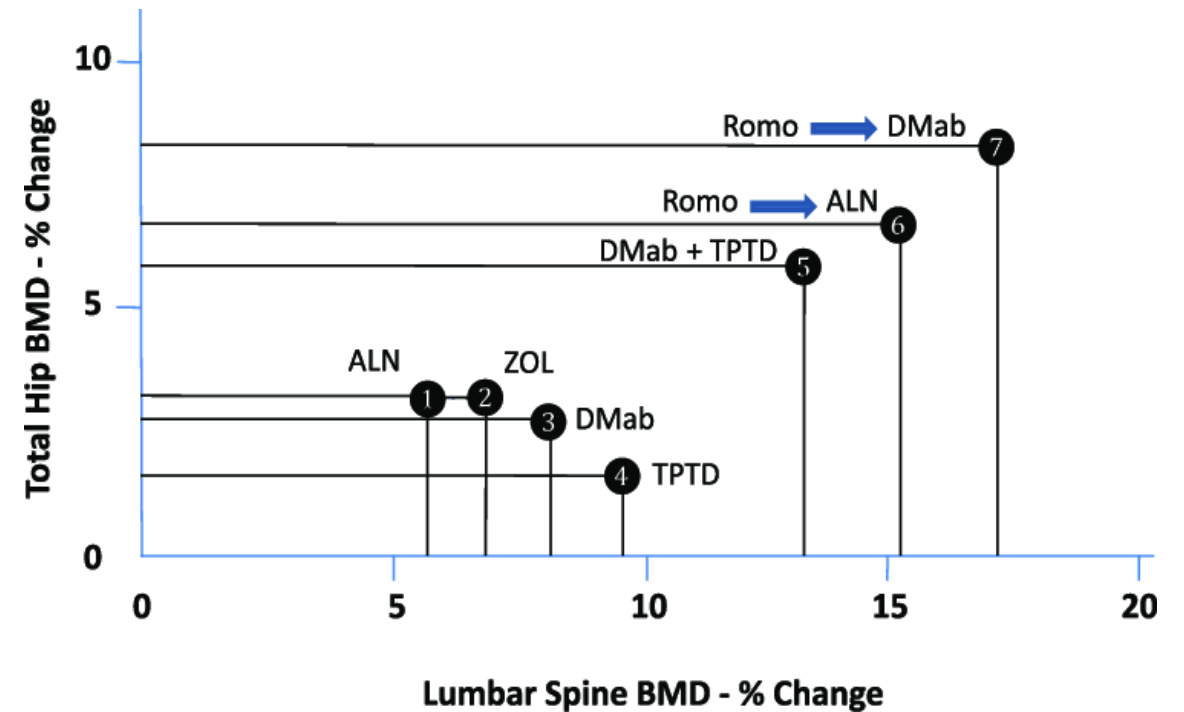


# Effectiveness

## Major Trials



## Treatment Effects



# Labs

141	101	12	95
4.3	27	0.76	

14.5	254
4.8	
43.9	

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



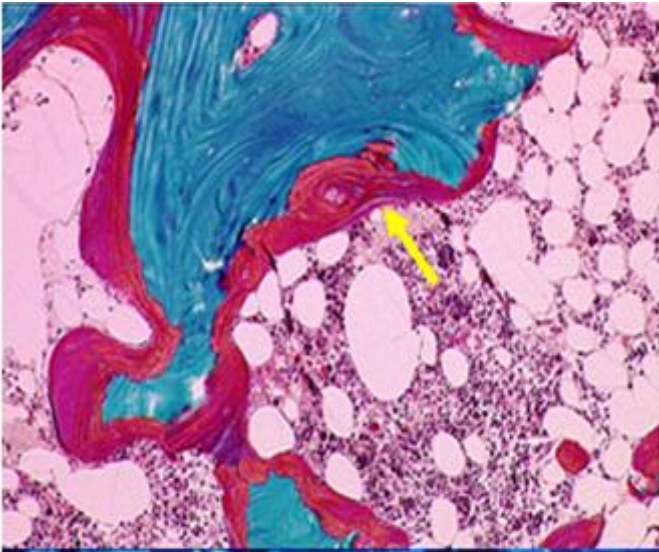
## Osteoporosis Resorption > Formation



## Impaired Mineralization Rickets/Osteomalacia



# Conditions with Mineralization Defects



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



# Labs

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4.3	27	0.76	

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43.9	
4.8	

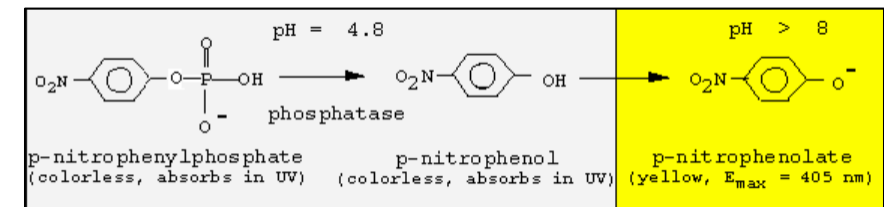
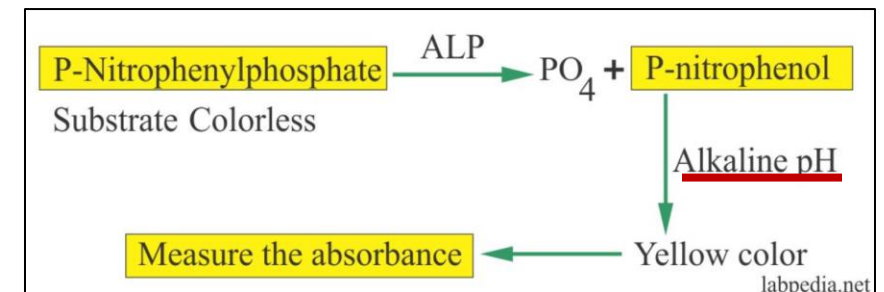
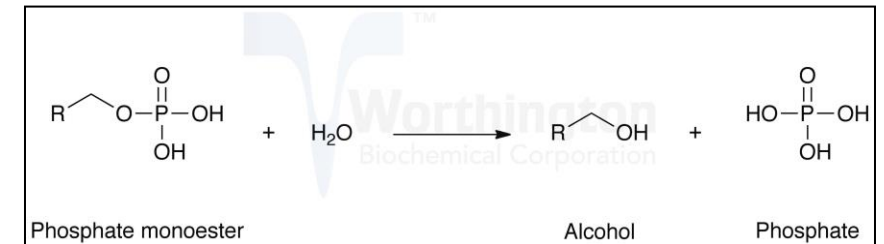
Ca 10.1  
Alb 4.8  
Phos 4.0

Vitamin D 34  
PTH 34  
24hr: Ca 245 mg  
Crt 1.1 g  
TV 1.9 L

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

# Alkaline Phosphatase

- Group of phosphatases
- Catalyze monoester phosphorylase reaction
- Optimal effect in alkaline environment
  - Assay requires pH > 8
- But **function at physiologic pH**
- Require Zn<sup>+</sup> and Ca<sup>+</sup> as co-factors



**pH > 8**

# Component of “Liver Function Test”

## LFT Interpretation

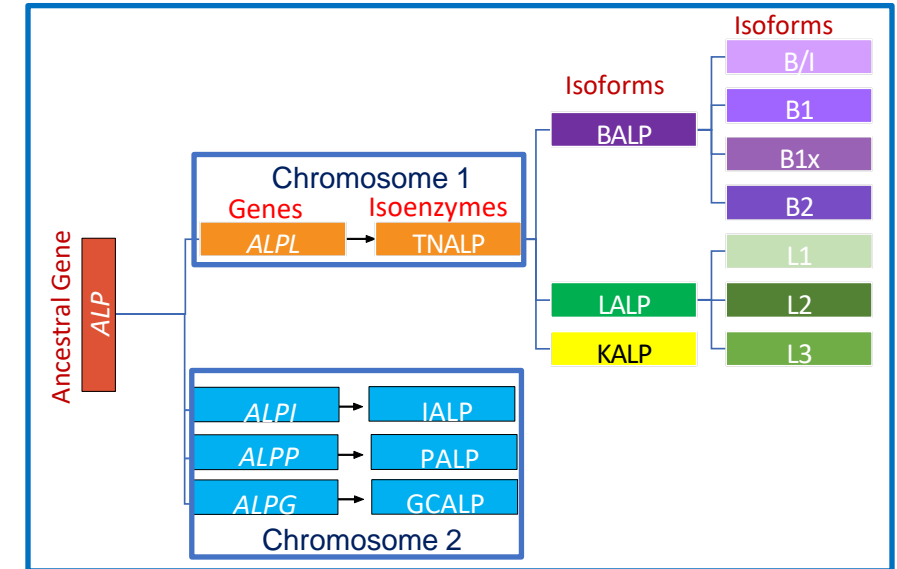
- Hepatocellular injury
  - $\uparrow$ AST & ALT  $\pm$   $\uparrow$  bili & A $\phi$ 
    - If  $\downarrow$  A $\phi$ - Wilson's
- Cholestasis
  - $\uparrow$  Bili & A $\phi$   $\pm$   $\uparrow$ AST & ALT
- Infiltrative
  - $\uparrow$  A $\phi$ , near normal bili, AST & ALT

## Bone Specific Component: ~20-60% of total A $\phi$

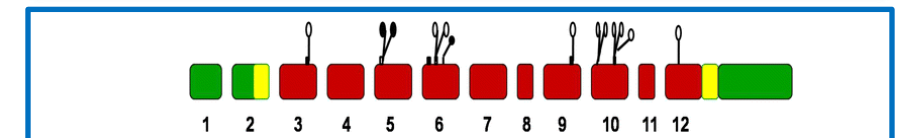
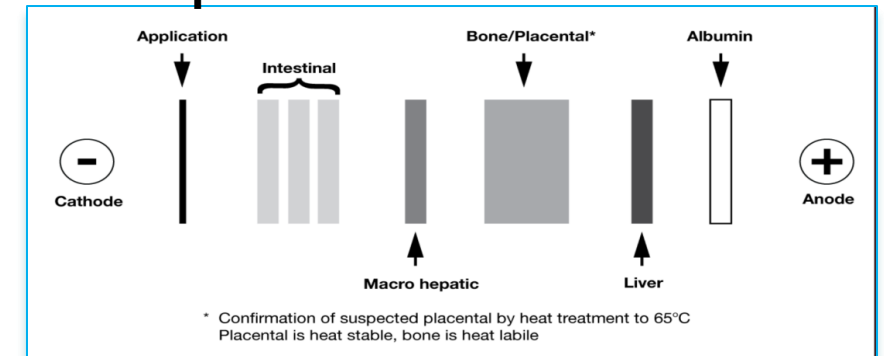
- Increase in bone fraction
  - Paget's disease of bone
  - Malignancies
    - PTHrP
    - Osteosarcomas
    - Osteoblastic mets
  - Anabolic bone agents
    - Romosozumab, PTH analogs
  - Hyperparathyroidism
  - Hyperthyroidism

# 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* - 1p34)
  - Different isoforms
    - Bone – most heat labile
    - Liver
    - Kidney

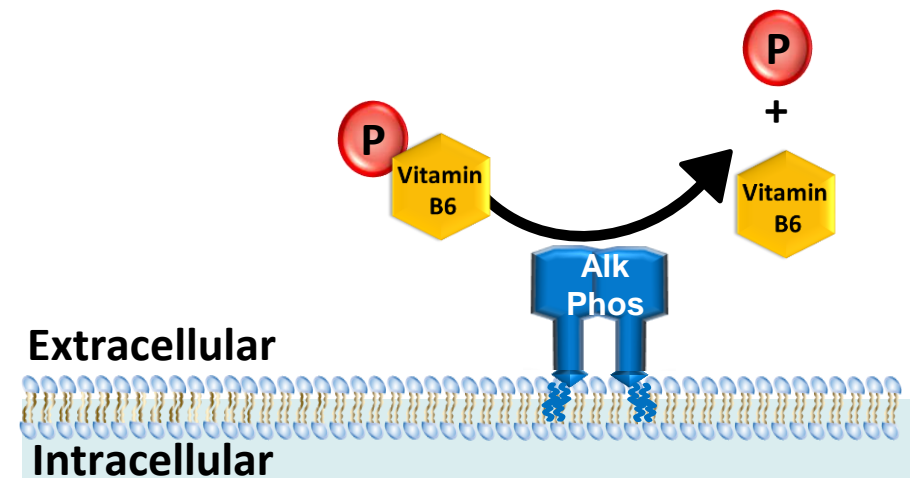
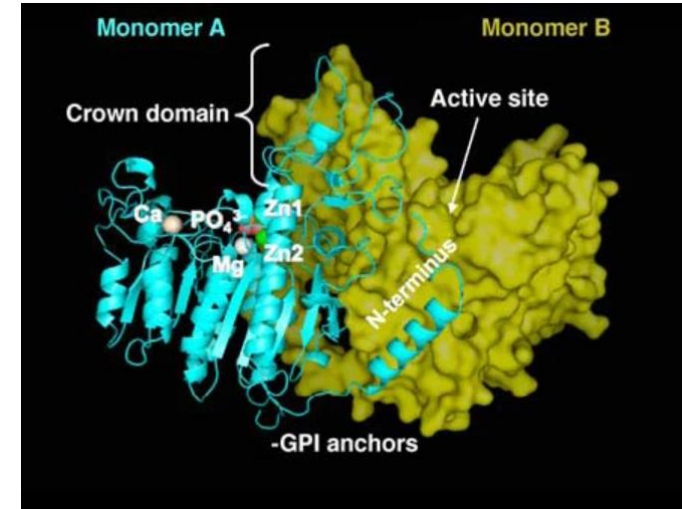


## Electrophoresis



# Alkaline Phosphatase

- Ectoenzymes
- GPI anchors
- Homodimers
- Require  $\text{Zn}^{+}$  and  $\text{Mg}^{+}$  as co-factors
- Many substrates



# Alk Phos Varies by Ethnicity & Gender

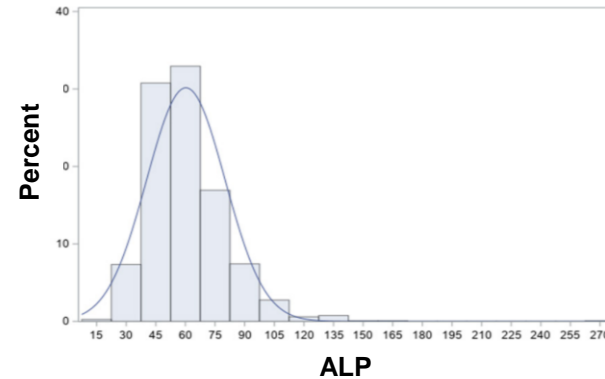
- NHANES Population Alk Phos measurement

- N=1199 (673 F/ 526 M)

- Mean: 60.2 IU

- Median: 57 IU

- Q1 47/ Q3 69



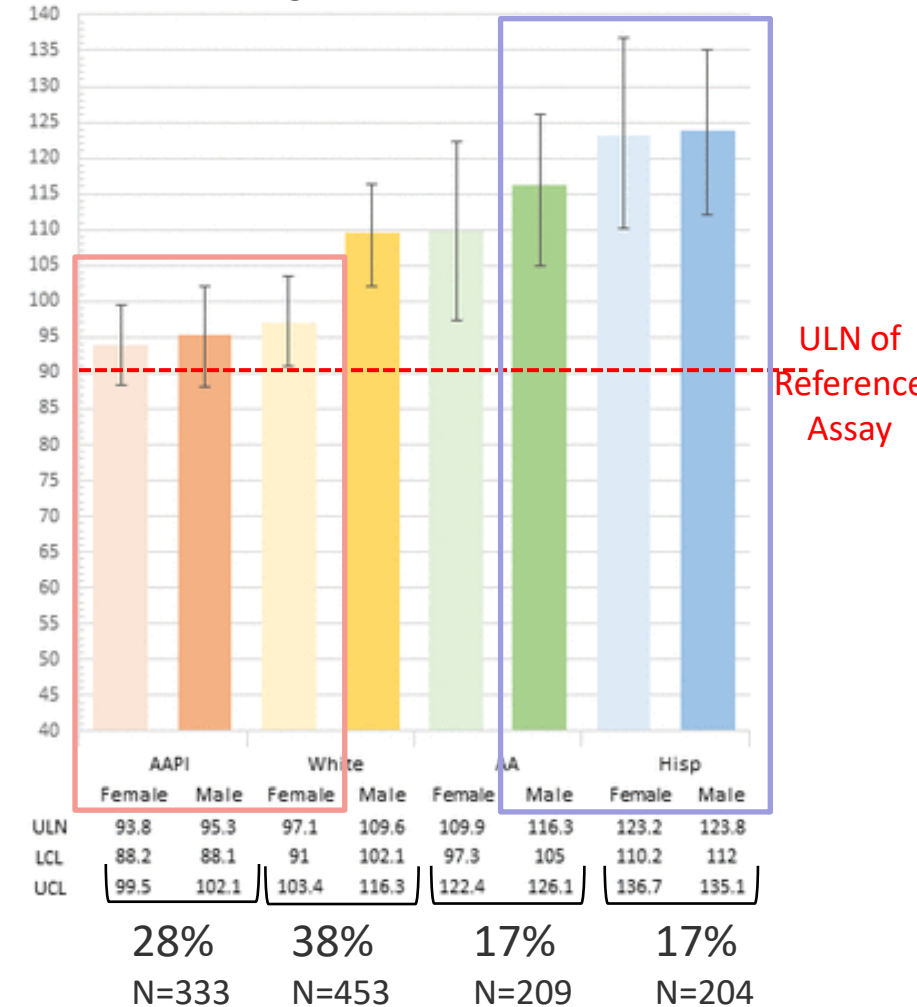
- Upper limits of normal

- Varies by ethnicity but with significant overlap

- Asian & White F < Hispanic & Black M

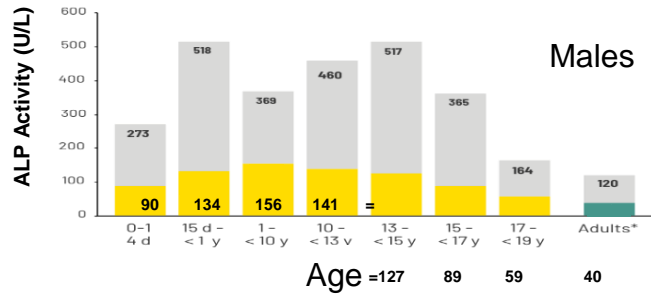
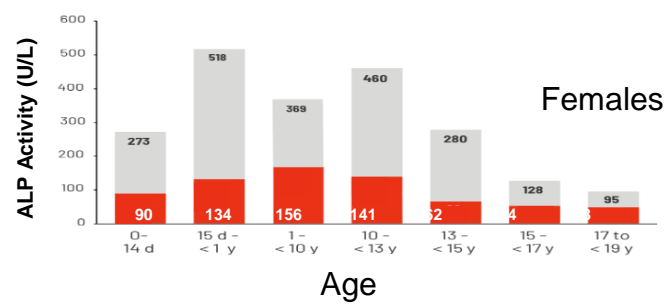
- Trend for males > females

Upper Range of Population Sample

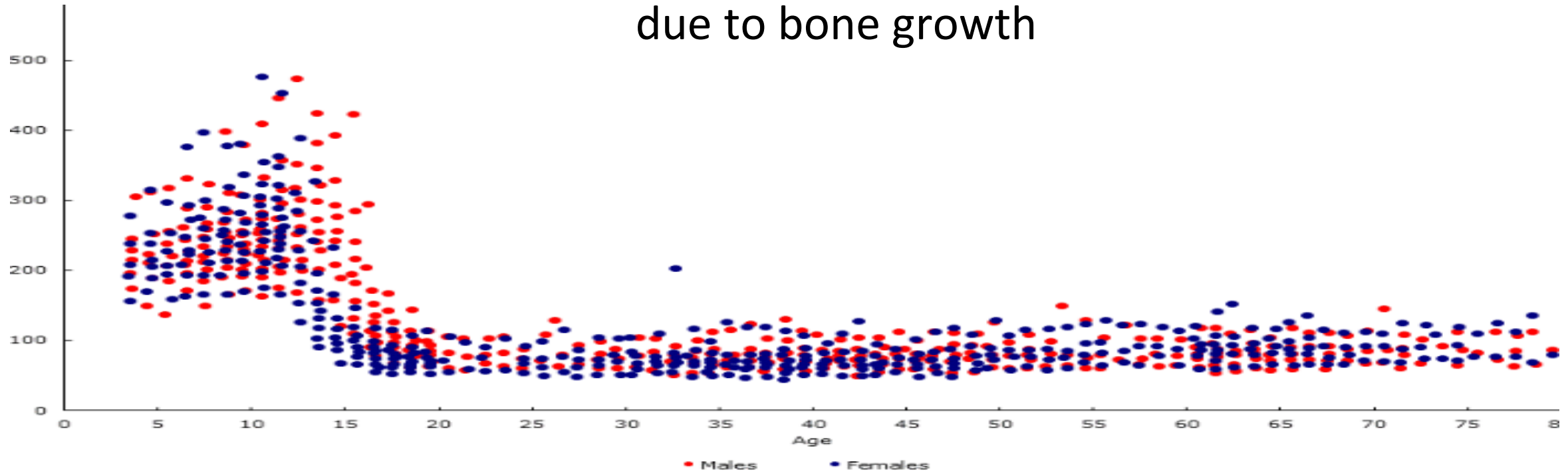


NHANES Population Distribution

# Alk Phos Varies by Age

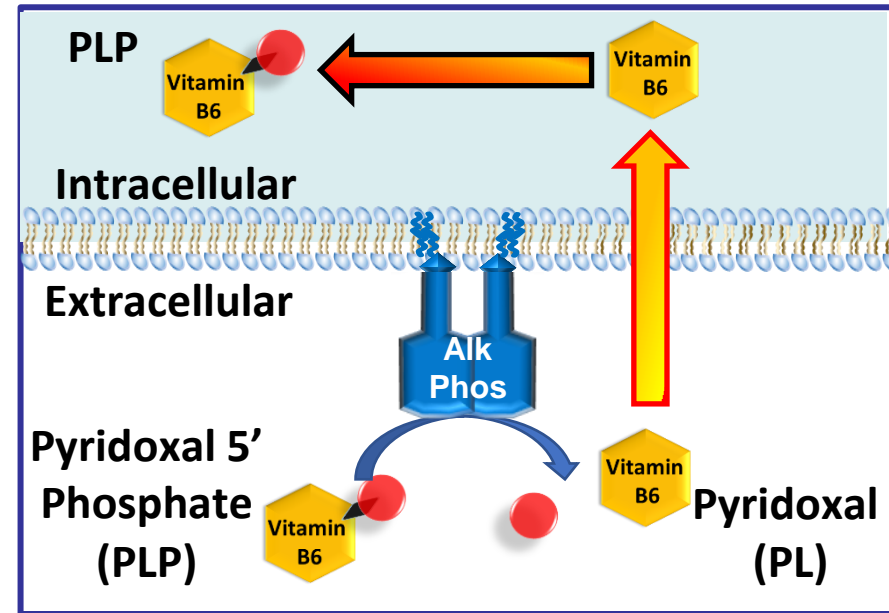
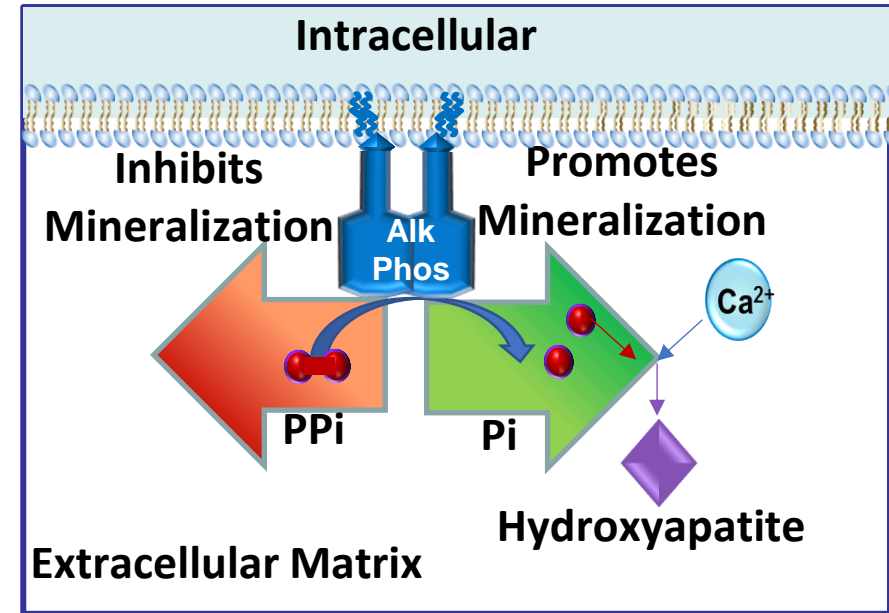


- Increased alk phos in children/young adults due to bone growth



# TNSALP Function: Overview

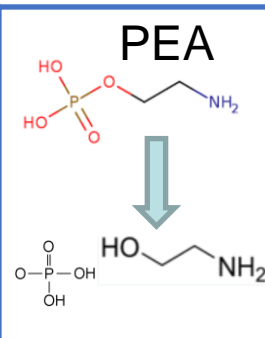
- Bone
  - Promotes mineralization
    - Hydrolyzes **inhibitors** of mineralization
- Nerves
  - Vit B6 transport into cells
    - Dephosphorylate PLP to PL to cross membrane



## Liver (Marker)

### PEA metabolism

Phosphoethanolamine  
to ethanolamine + Pi





# Low Alkaline Phosphatase

**Table 1.** Differential Diagnosis of Hypophosphatasemia Based on the Temporal Evolution of the Low Serum ALP Value<sup>(6)</sup>

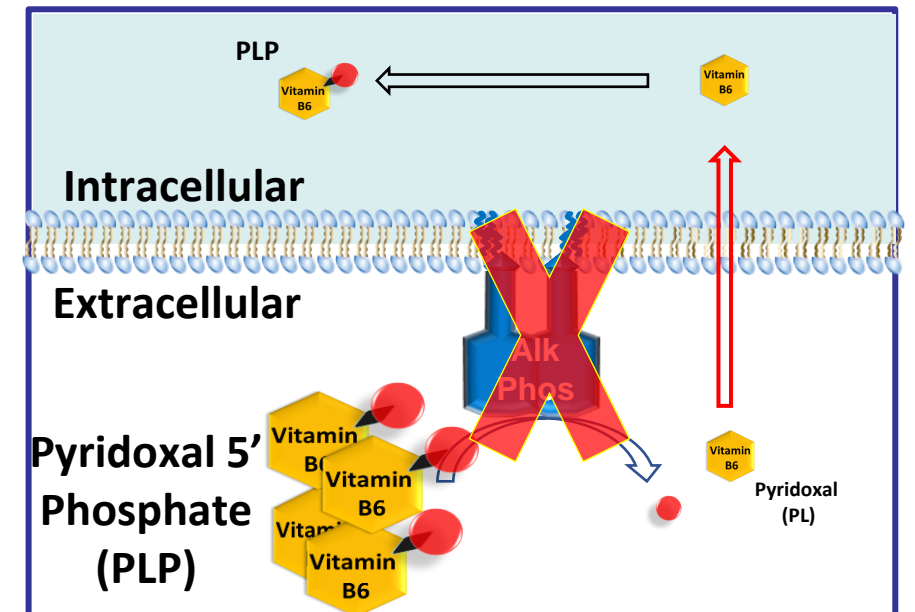
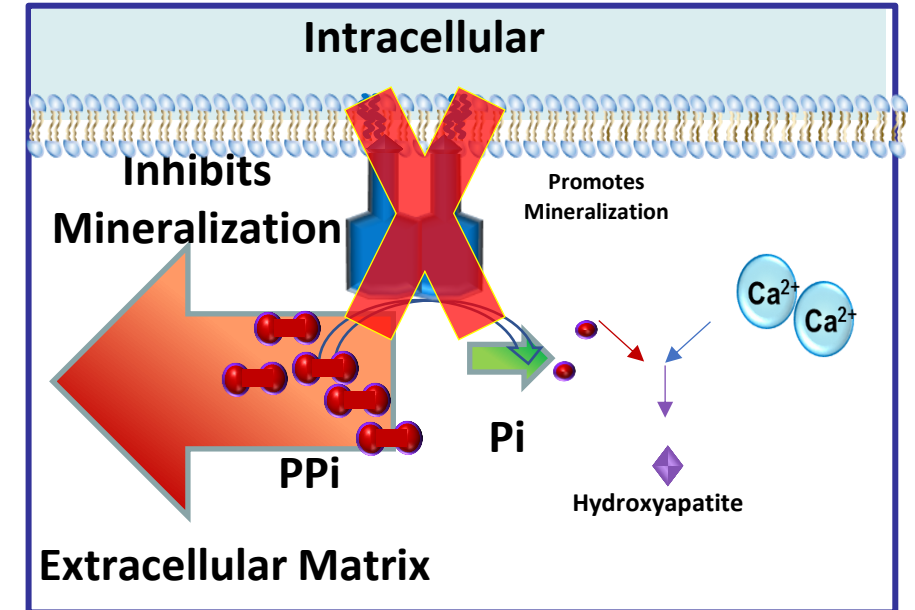
Temporal evolution of the low serum ALP value		
Persistently low	Transiently low	Precipitously low
<ul style="list-style-type: none"><li>• Hypophosphatasia (HPP: OMIM 146300,241500,241510)</li><li>• Cleidocranial dysplasia (OMIM166210)</li><li>• Mseleni joint disease (OMIM 613342)</li></ul>	<ul style="list-style-type: none"><li>• Osteogenesis imperfecta type II (OMIM 166210)</li><li>• Profound hypothyroidism</li><li>• Cushing’s disease</li><li>• Bisphosphonate therapy</li><li>• Adynamic renal osteodystrophy</li><li>• Milk-alkali syndrome</li><li>• Vitamin D intoxication</li><li>• Wilson’s disease</li><li>• Nutritional deficiencies (Vit C)</li><li>• Hypomagnesemia</li> <li>• Hypozincemia</li><li>• Celiac disease</li><li>• Pernicious anemia</li><li>• Radioactive heavy metal contamination</li></ul>	<ul style="list-style-type: none"><li>• Cardiac bypass surgery</li> <li>• Major trauma</li><li>• Major surgery</li><li>• Cancers and chemotherapy</li><li>• Multiple myeloma</li><li>• Transfusion (often massive)</li><li>• Starvation/acute caloric restriction</li><li>• Sepsis/multi-organ/hepatic failure</li><li>• Analytic error</li><li>• Improperly collected specimen (eg, EDTA, citrate, oxalate)</li></ul>

# Low Alkaline Phosphatase

- Hypophosphatasia
- Assay Interference
  - Wilson disease (excess copper)
  - $\text{Zn}^{+2}$  or  $\text{Mg}^{+2}$  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
    - Raloxifene, sex steroids
  - Multiple myeloma
  - Cardiac bypass/ trauma/critical illness
  - Starvation/malnutrition
    - Celiac disease
- Other
  - Pernicious/profound anemia
  - Vitamin C deficiency

# 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



# Clinical Subtypes

## Perinatal Benign & Severe

### 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



### Juvenile

- **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



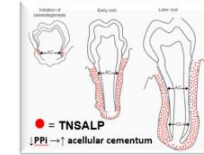
### Adult

- 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



### Odontohypophosphatasia

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



Zweifel Int J Oral Sci. 2015

# Clinical Subtypes

1:300K  
Autosomal Recessive

1:7K - 1:500  
Autosomal Dominant



Perinatal

6 mo

18 yr

Infantile

Juvenile

Adulthood

## Perinatal

- Severe hypomineralization
  - Rachitic changes
  - Accordion limbs
  - Fractures
- Craniosynostosis
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## Infantile

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- 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



## 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



# Adult Patients with HPP

1:300K  
Autosomal Recessive

1:7K - 1:500  
Autosomal Dominant



Perinatal Infantile Juvenile

18 yr

Adulthood

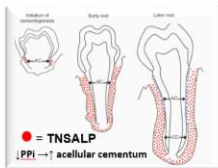
Perinatal

Infantile

Childhood

**Odontohypophosphatasia**

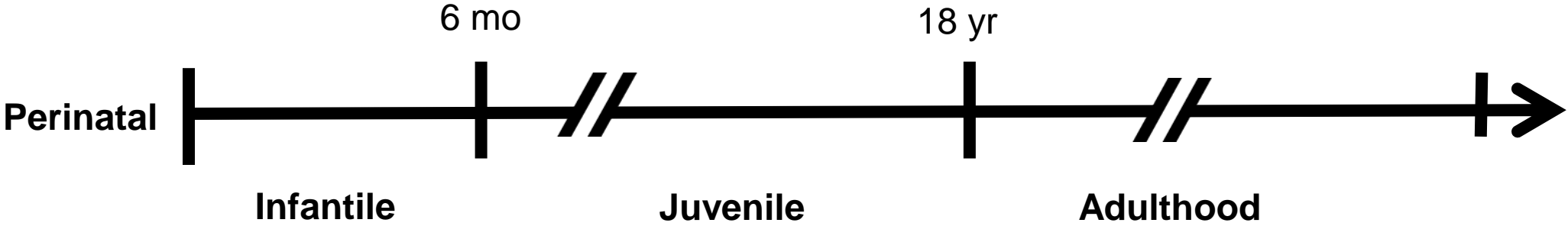
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  - ↓ Cementogenesis



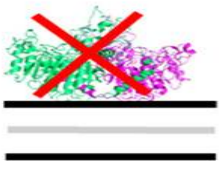
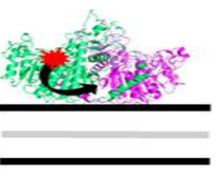
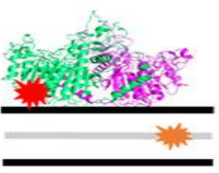
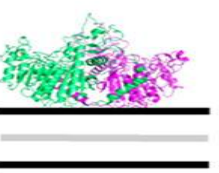
Zweffler Int J Oral Sci. 2015

- 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 <sub>DNE</sub>	AD <sub>haploinsuff</sub>	-
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 <sub>homoz</sub>	Sd/m, s/m, Sd/N	s/N, m/N	N/N

 <p>TNSALP COL1A1 COL1A2 COL1A1</p> <p>s/s</p>	 <p>TNSALP COL1A1 COL1A2 COL1A1</p> <p>Sd/N</p>	 <p>TNSALP COL1A1 COL1A2 COL1A1</p> <p>s/N</p>	 <p>TNSALP COL1A1 COL1A2 COL1A1</p> <p>N/N</p>
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# Clinical Manifestations

- **Skeletal**

- Rickets/osteomalacia
- Craniosynostosis
- Non-healing fractures
- Chronic bone pain

- **Renal**

- Nephrocalcinosis
- Kidney stones

- **Rheumatologic**

- Chondrocalcinosis/CPPD
- Progressive arthritis

- **Neurologic**

- Seizures
- Neuropathy
- Anxiety/ depression

- **Muscular**

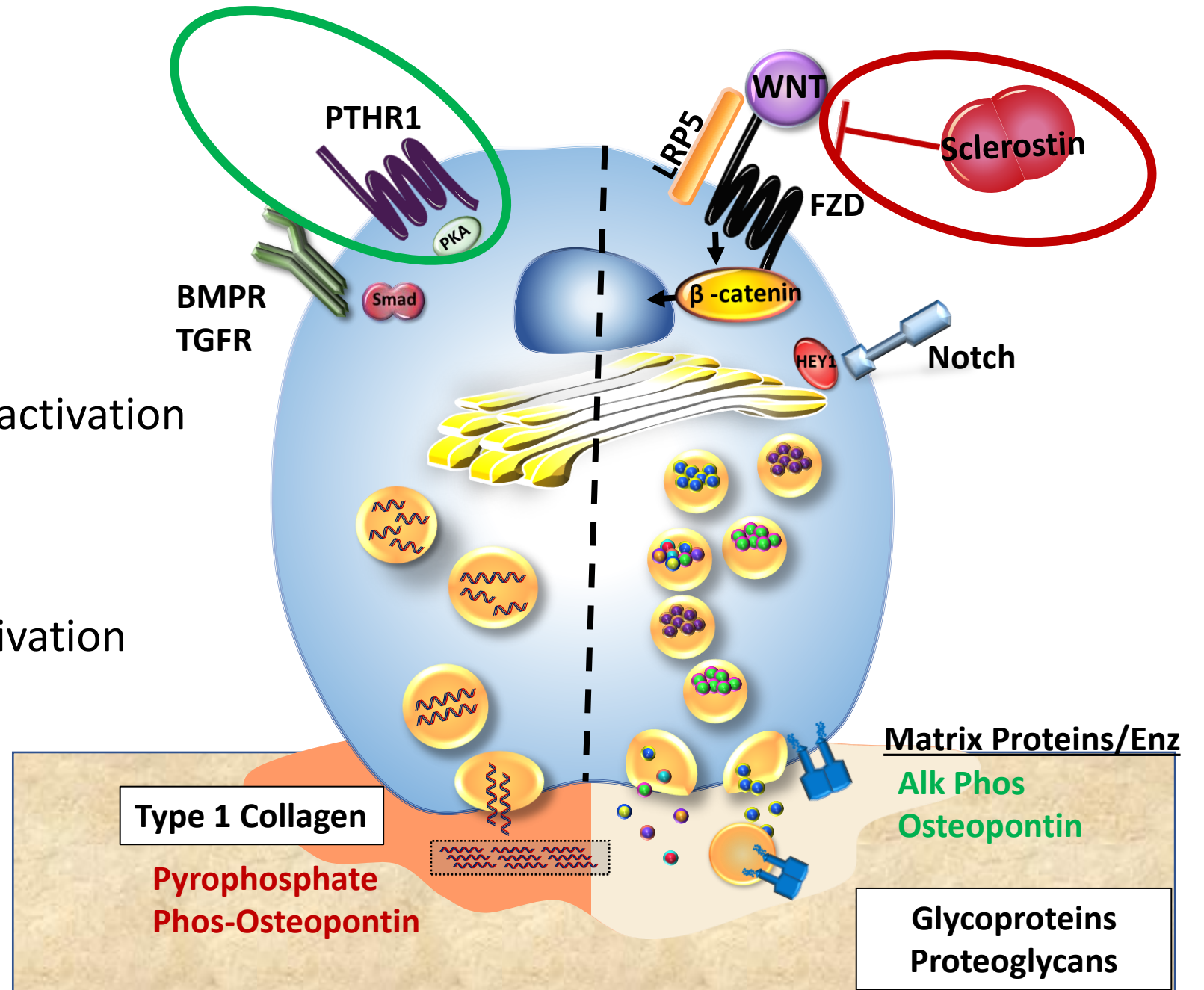
- Myopathy
- Myalgias
- Weakness
- Impaired ambulation

- **Dental**

- Early tooth loss

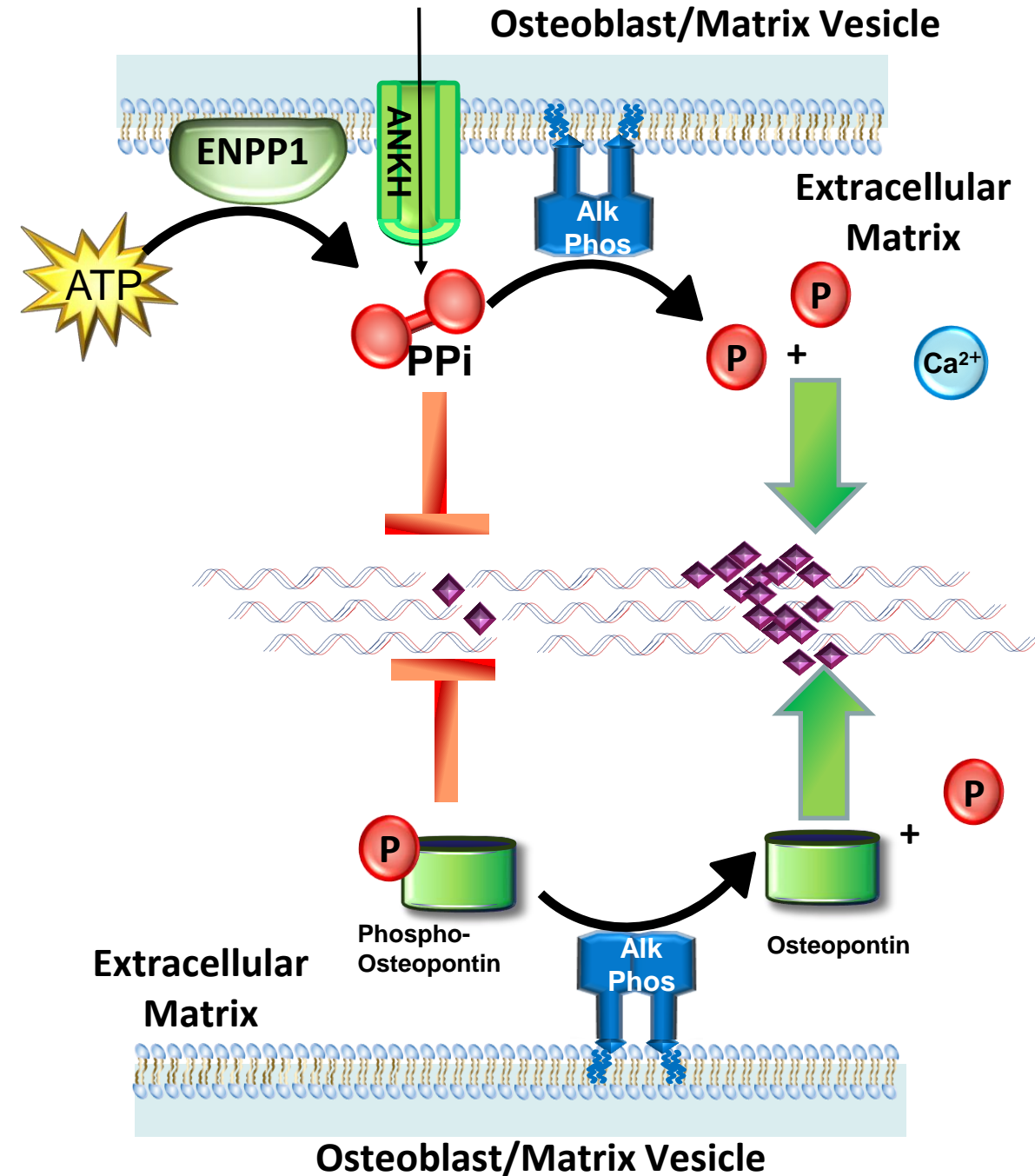
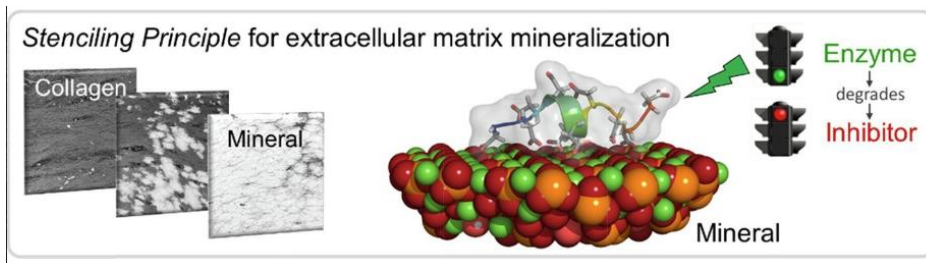


- **PTH Receptor**
  - Stimulates osteoblast activation
- **Sclerostin**
  - Inhibits osteoblast activation



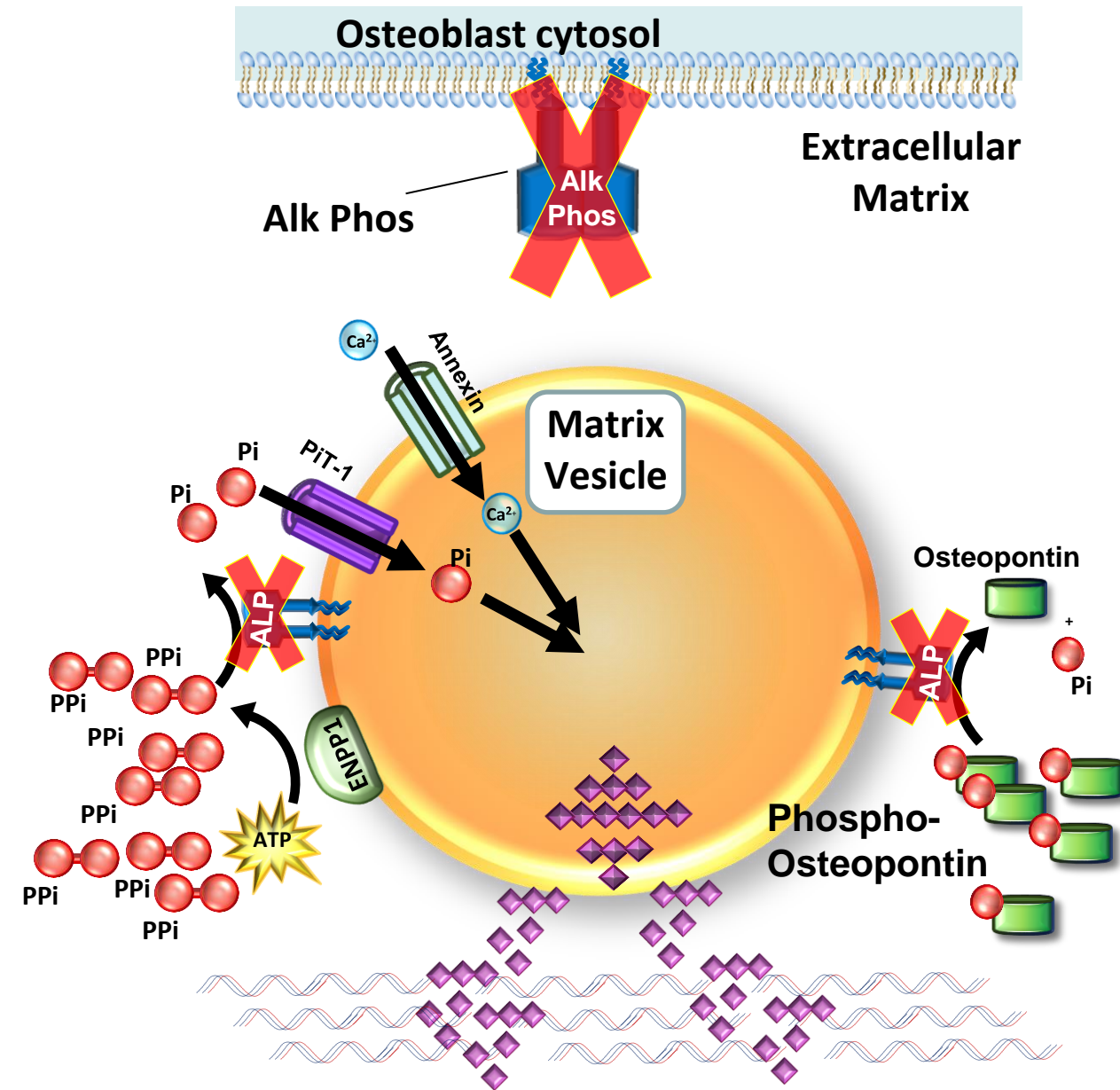
# Bone Mineralization

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



# 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

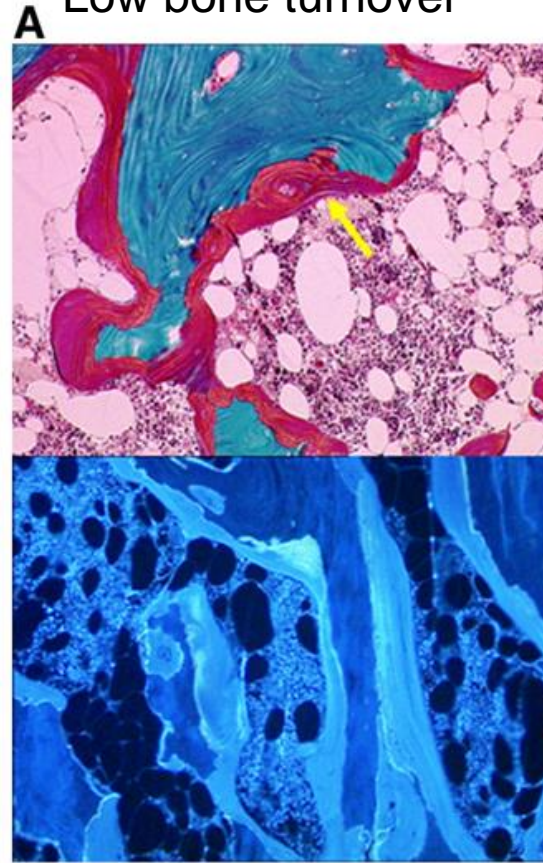




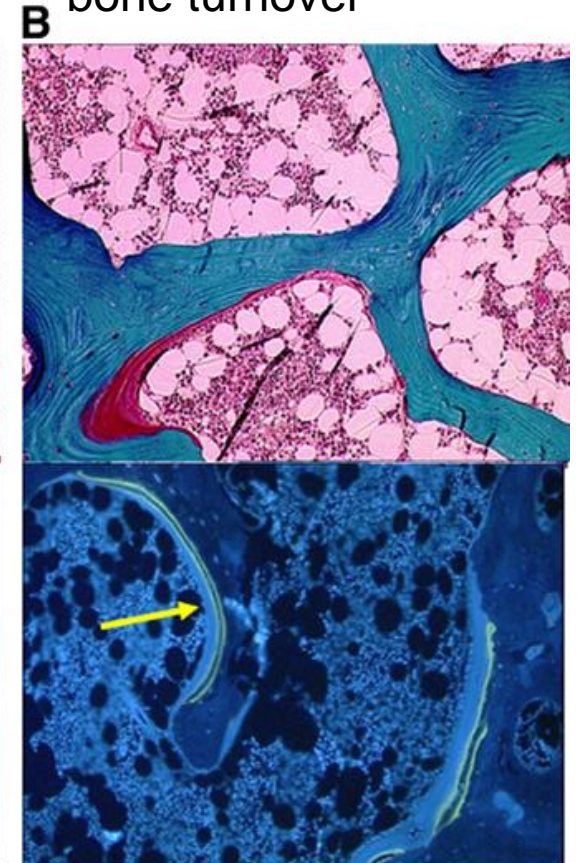
# Adults with HPP Have Variable Mineralization Defects



Osteomalacia /  
Low bone turnover

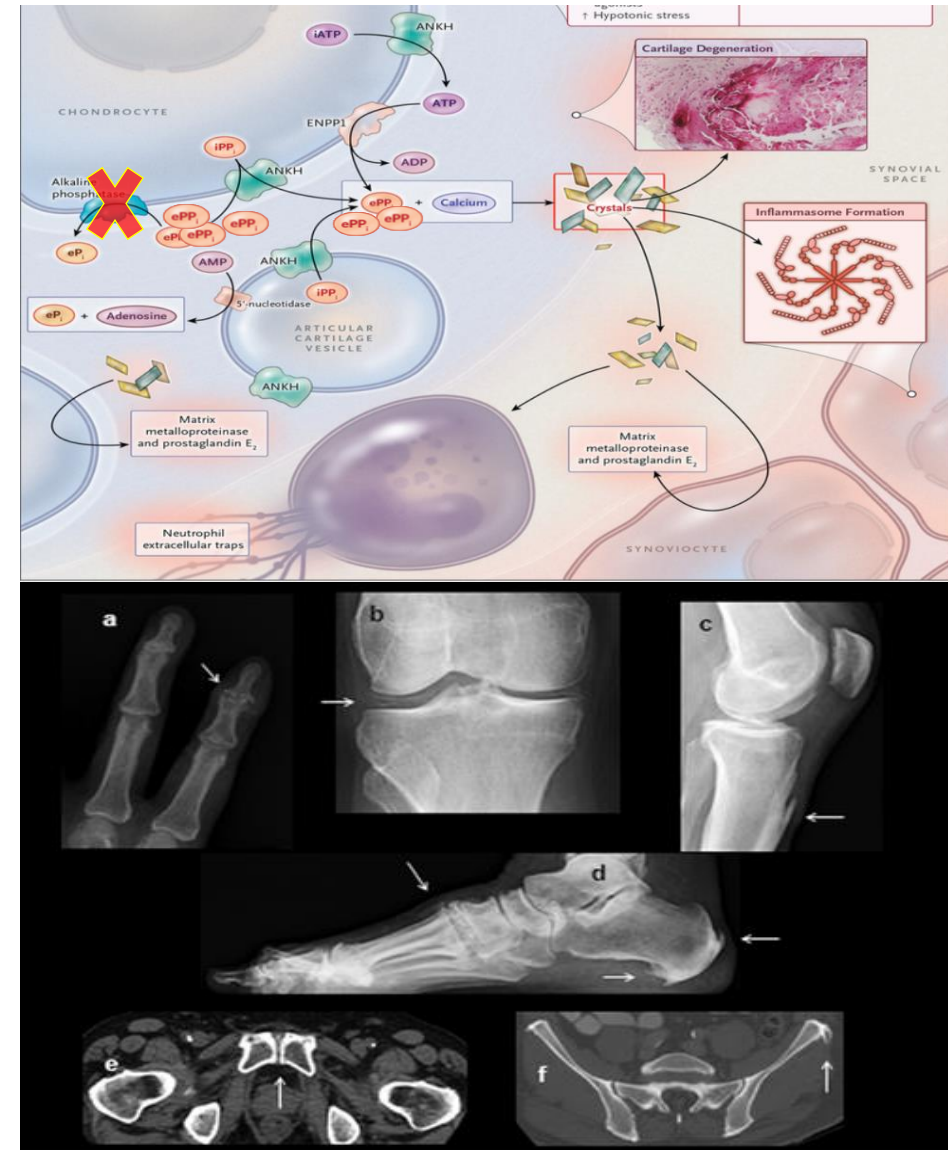


Normal mineralization &  
bone turnover



# 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  $\phi$ :**

- **2 Major Criteria**

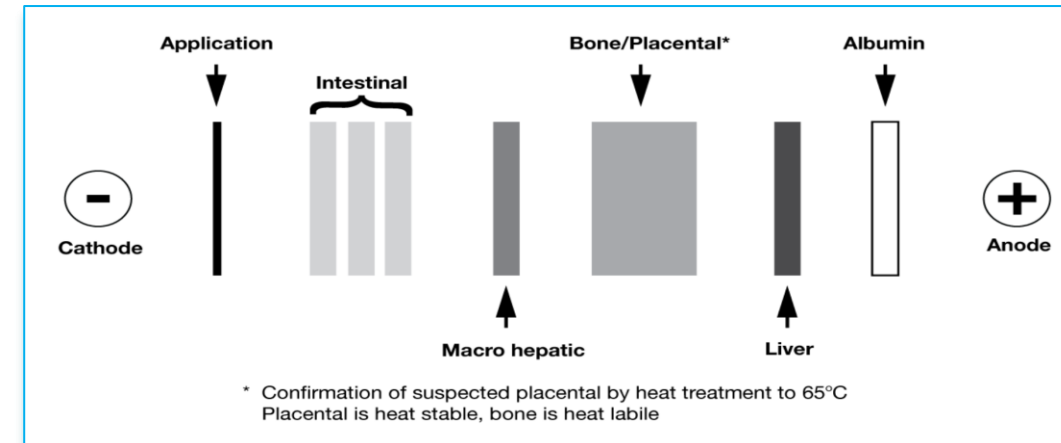
**OR**

- **1 Major +2 Minor**

# 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 A $\phi$  (TNSALP)  
Normal Intestinal A $\phi$  - higher percentage of total



**Electrophoresis**

# Diagnosis of Hypophosphatasia

- **Major Criteria**

- *ALPL* gene variant
- ↑ Natural substrates
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  - 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

- **Heterozygous pathogenic nonsense p.Tyr101\***

- **↑Vit B6 (PLP) 109-227** [5-50 µg/L]
- **↑ Urine PEA 65-98** [<48 nmol/mg Creat]

- **2 metatarsal fractures**

- **Recurrent fractures after ORIF**

- **Fibromyalgia**

- **Lost primary teeth @4 yo**

- **CaPyrophosphate crystal deposition in hands & knees**

- Normal renal U/S

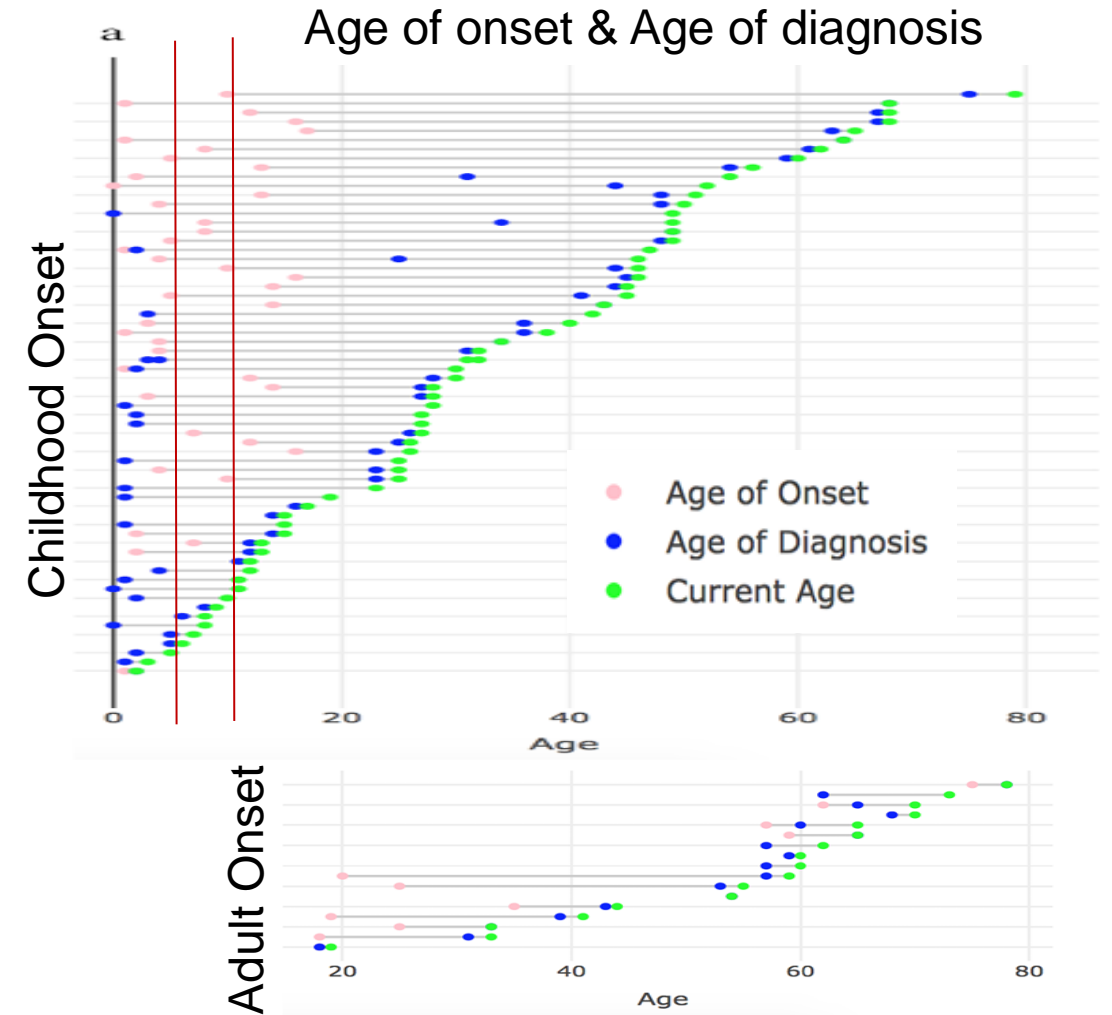
In adults w persistently low alk  $\phi$ :

- **2 Major Criteria** ✓
- OR
- **1 Major +2 Minor** ✓



# 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



# Treatment (Mineralization)

- Avoid
  - Excess Ca, vitD, Phos
    - Nephrocalcinosis
    - Ectopic calcifications
  - **Antiresorptives**
    - Case series with ↑ AFF
- Anabolics
  - Teriparatide/Abaloparatide
  - Romosozumab
- Enzyme replacement tx
  - Asfotase alfa

↓ **Alk Phos**

↑ **Alk Phos**

# Repeated Chair-Rise Test (Video)

27.5 seconds



12.5 seconds

