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connecting the dots of rare disease

SUPPORTING SUSPECT PATIENT RECOGNITION
FOR FURTHER CLINICAL EVALUATION

HPP Program Implementation Guide

HPP=hypophosphatasia.

ALEXION®
AstraZeneca Rare Disease

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EHR=electronic health record.

HPP is a rare, inherited, progressive metabolic bone disease caused by deficient alkaline phosphatase (ALP) enzyme activity. Due to the heterogeneity of HPP symptoms, diagnoses are often delayed or missed.[1,2] The objective of this guide is to help HCPs understand the clinical presentation of HPP and triage patients who may be suspected of having HPP for further HCP evaluation to diagnose or rule out the disease. Specifically, the program will make use of relevant patient history data, disease codes, suspect patient lists, and BPAs.

Key sections

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   An overview of the clinical criteria required for HCPs to diagnose HPP based on published literature. Diagnostic criteria are consistent across age groups. However, key differences in clinical signs and symptoms are outlined for the perinatal period (*in utero* or at birth), infants, children, and adults.

2. **Generating suspect HPP patient lists** ..... Page 4
   A comprehensive guide to generating a suspect patient list for HPP in the perinatal period, infants, children, and adults, based on relevant clinical characteristics.

3. **BPAs to help triage a suspect HPP patient** ..... Page 6
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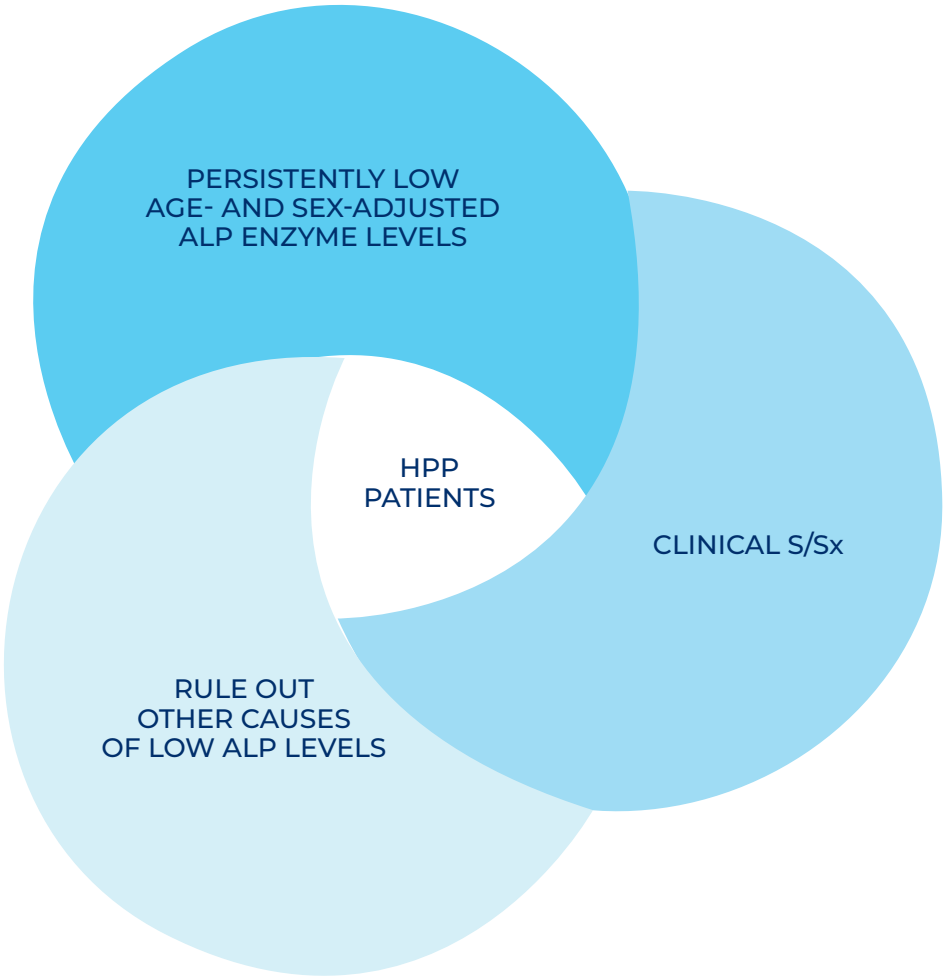
BPA=best practice alert; EHR=electronic health record; HCP=healthcare provider; HPP=hypophosphatasia.

Clinical criteria for HPP

HPP is a rare disease that has inherent challenges associated with diagnosis.[1,2] A range of perplexing signs and symptoms may appear with varying severity at different ages, many of which can be overlooked by HCPs.[1] The following diagnostic criteria can be used by HCPs to triage suspect HPP patients for further evaluation and diagnosis.

1. Clinical criteria for HPP (all age groups)[2-4]



IMPORTANT NOTE: While EHR systems may assist providers in generating suspect lists, it is the sole responsibility of the HCP to make a diagnosis based on in-person patient evaluation.

ALP=alkaline phosphatase; S/Sx=signs and symptoms.

Diagnostic criteria

The criteria used to help inform an HPP diagnosis includes the following: **identify persistently low age- and sex-adjusted ALP levels, investigate clinical signs and symptoms of HPP, and rule out other causes of low ALP levels.**

Persistently low age- and sex-adjusted ALP levels detected[3-6]

The biochemical hallmark of HPP is persistently low age- and sex-adjusted ALP levels. Persistently low levels may be defined as at least 2 values below normal within 6 months. Laboratory ALP reference ranges should be adjusted for age and sex.

Investigation of clinical signs and symptoms of HPP[2,7]

HPP symptoms can present at any age and may be progressive. Recognizing key symptoms in the presence of persistently low ALP can help inform an HPP diagnosis.

Adult HPP (>18 years) clinical signs and symptoms

Please Note: Pediatric signs and symptoms listed below may also appear in adult patient medical histories.

- Dental abnormalities (tooth loss, destruction of periodontal tissue)[1,5,7]
- Fractures (low trauma fractures, delayed healing or recurrent fractures, pseudofractures, and metatarsal stress fractures)[5,7,8]
- Skeletal deformities[5,7,8]
- Short stature[5,7,8]
- Osteomalacia[5,7,8]
- Impaired mobility[9]
- Gait disturbance[8]
- Joint hypermobility[9]
- Muscle weakness[8]
- Fatigue[10]
- Pain (bone, muscle, and/or joint)[7,8,10]
- CPPD (calcium pyrophosphate deposition disease [pseudogout])[7,8,10]
- Nephrocalcinosis[2,7,11]
- Ophthalmic calcifications[2,7,11]
- History of rickets[2,4]

Pediatric signs and symptoms (may also appear in adult patient medical histories)

Key differences between adult HPP clinical signs and symptoms and those for the perinatal period, infants, and children are outlined below.

Perinatal HPP (*in utero* or at birth) signs and symptoms[5,7,11]

Perinatal HPP patient recognition comprises clinical signs and symptoms associated with the fetus (*in utero* or at birth), including, but not limited to, what is outlined below.

- Skeletal deformities (including shortened or bowed limbs or enlarged wrists, knees, and ankles)
- Hypoechogenic/hypomineralized skull
- Short, beaded, or thin ribs
- Inconsistent ossification of vertebrae
- Shortening, bowing, angulation of long bones
- Reduced mineralization of hands
- Deficient or absent ossification of bones
- Metaphyseal radiolucencies
- Fractures/low trauma fractures
- Clubfoot
- Osteochondral spurs (Bowdler spurs)
- Ectopic calcification (including nephrocalcinosis and ophthalmic calcification)
- Stillbirth
- Severe chest deformity
- Seizures
- Apnea

Infantile HPP (birth to <6 months) signs and symptoms[5,7,11]

Infantile HPP patient recognition comprises clinical signs and symptoms associated with an infant from birth to <6 months, including, but not limited to, what is outlined below.

- Rickets
- Fractures/low trauma fractures
- Hypercalcemia/hypercalciuria
- Ectopic calcification (including nephrocalcinosis and ophthalmic calcification)
- Skeletal deformities including shortened or bowed limbs or enlarged wrists, knees, or ankles
- Craniosynostosis
- Hypotonia
- Poor feeding
- Poor weight gain
- Failure to thrive
- Respiratory insufficiency
- Respiratory failure
- Vitamin B6 responsive seizures.

Diagnostic criteria (continued)

Pediatric signs and symptoms (may also appear in adult patient medical histories) (continued)

Childhood HPP (≥6 months to <18 years) signs and symptoms[5,7,11]

Childhood HPP patient recognition comprises clinical signs and symptoms associated with the fetus (*in utero* or at birth), including, but not limited to, what is outlined below.

- Rickets
- Premature loss of primary teeth
- Low trauma fractures/poorly healing or recurrent fractures
- Skeletal deformities, including shortened or bowed limbs or enlarged wrists, knees, or ankles
- Craniosynostosis
- Ectopic calcification
- Delayed walking
- Waddling gait
- Delayed/missed motor milestones
- Pain (bone, muscle, and/or joint)
- Short stature
- Muscle weakness.

Rule out other causes of low ALP levels[2,4]

To make an HPP diagnosis, HCPs should rule out other causes of low ALP. Below is a list of other potential causes of low ALP.

Other causes of low ALP levels[4,*,†]

- Cleidocranial dysplasia/dysostosis
- Mseleni joint disease
- Benign familial hypophosphatasemia
- Osteogenesis imperfecta type II
- Profound hypothyroidism
- Cushing's disease
- Bisphosphonate therapy
- Adynamic renal osteodystrophy
- Milk-alkali syndrome
- Vitamin D intoxication
- Wilson disease
- Nutritional deficiencies (vitamin C)
- Hypomagnesemia
- Hypozincemia
- Celiac disease
- Pernicious anemia
- Radioactive heavy metal contamination
- Cardiac bypass surgery
- Major trauma
- Surgery
- Cancers and chemotherapy
- Multiple myeloma
- Blood transfusion
- Starvation/acute caloric restriction
- Sepsis/multi-organ/hepatic failure
- Analytic error
- Improperly collected specimen (eg, Ethylenediaminetetraacetic acid [EDTA], citrate, oxalate)

Additional tests

If patients present with any of the above clinical signs and symptoms plus persistently low ALP, after ruling out other causes of low ALP, there is sufficient evidence for an HPP diagnosis.

The following laboratory tests can further support the HCP's diagnosis of HPP.

Serum PLP/Vitamin B6 levels

- In HPP, low ALP may lead to an accumulation of PLP[5]
- PLP is the major circulating form of vitamin B6
- Levels may be high or normal*

**Special care must be taken to ensure the sample is not exposed to light during collection, as it can alter the results.*[12]

Urinary PEA levels

- The role of PEA in HPP has not been fully established[5]
- PEA levels are assessed by collecting a urine sample; however, the preferred method of collection varies (eg, spot vs 24-hour urine sample). Please consult with the specific laboratory to discuss sample type, duration and timing of collection, as urinary protein levels can vary throughout a 24-hour period[7,13]

Genetic testing

- The HCP may elect to obtain genetic testing to look for mutations in the *ALPL* gene
- Mutations in the *ALPL* gene cause low ALP activity[5,7]
- If the genetic test is negative or inconclusive, the diagnosis of HPP is not necessarily excluded; the test result may arise from mutations of unknown significance or mutations that are undetectable because they lie in intronic or regulatory sequences for other genes[14]
- Although genetic testing of the *ALPL* gene is not required for an HPP diagnosis, it may be useful for genetic counseling purposes[15]

PEA=phosphoethanolamine; PLP=pyridoxal 5'-phosphate; PPi=inorganic pyrophosphate.
*ALP levels adjusted for age and sex.
†Not an exhaustive list.

Generating suspect HPP patient lists

2

In HPP, patients are often either undiagnosed or misdiagnosed.[1,16] This toolkit may help reduce the incidence of undiagnosed and misdiagnosed patients by utilizing the EHR and evidence-based diagnostic criteria to generate suspect patient lists that may help increase awareness of potential HPP patients for further evaluation by HCPs.

2. Generating the suspect HPP patient list in the EHR[2,4,11]

Generating the suspect patient list requires utilizing the same clinical criteria that HCPs can use for making an HPP diagnosis. How these elements may be used behind the scenes with the EHR is outlined below.

ALL PATIENTS

LOW ALP LEVELS

- A suspect patient list begins with persistently low (2 or more within 6 months) ALP levels in the laboratory results section
  - » Lab results for ALP levels can be captured in the EHR
  - » Check with your lab for age- and sex-adjusted reference ranges or follow institutional policies for defining low ALP values
- If patients meet the criteria for persistently low ALP, they will continue to the next criterion

PATIENTS WITH PERSISTENTLY LOW ALP LEVELS*

CLINICAL S/Sx

- The resulting patients proceed to the next criterion: patients who exhibit the clinical signs and symptoms of HPP in either their current health record or medical history
  - » To capture this, patient data are run through a diagnostic filter utilizing ICD-10 and SNOMED codes for clinical signs and symptoms of HPP

PATIENTS WITH PERSISTENTLY LOW ALP LEVELS* AND CLINICAL SIGNS AND SYMPTOMS OF HPP

RULE OUT OTHER CAUSES OF LOW ALP LEVELS

- In the final funnel, the resulting patients' data will be searched for these other conditions that may cause low ALP levels, utilizing the ICD-10, SNOMED, and CPT-10 codes
- Patients for whom these codes are found do not continue on to the suspect HPP patient list[4]

PATIENTS WITH PERSISTENTLY LOW ALP LEVELS*, S/Sx OF HPP, AND NO OTHER CAUSES FOR LOW ALP LEVELS

SUSPECT PATIENT LIST

IMPORTANT NOTE: While EHR systems may assist providers in generating suspect lists, it is the sole responsibility of the HCP to make a diagnosis based on in-person patient evaluation.
It is important to indicate that the final suspect list of patients will be sent to the HCP(s) for review. Including criteria for a suspect patient list helps explain to the HCP why the patient is on the report.

S/Sx=signs and symptoms.
*Refer to your lab for appropriate age- and sex-adjusted reference range.

BPAs to help triage a suspect HPP patient

3. BPAs to help triage a suspect HPP patient

Use suspect patient criteria and the diagnostic best practices to create alerts

Using the data in the EHR to surface information in a patient's health record can be the first step in recognizing a suspect HPP patient. Generating BPAs requires utilizing the same clinical criteria that HCPs use for making an HPP diagnosis: identifying persistently low ALP levels*, recognizing key clinical signs and symptoms of HPP, and ruling out other causes of low ALP levels.

BPAs can be created using clinical criteria and the data in the EHR to help alert and guide an HCP. There are several points where alerts may be set. Examples are shown below for the diagnostic criteria and suspect patients.

A BPAs for suspect HPP patients

If patients have met these criteria, sufficient evidence should be present to help the HCP determine if an HPP diagnosis is appropriate. However, should the HCP wish to further confirm their findings, the following tests may support the presence of HPP: vitamin B6/serum PLP levels, urinary PEA levels, and *ALPL* genetic testing.[2-4,6]

B BPAs for vitamin B6/serum PLP and urinary PEA lab considerations

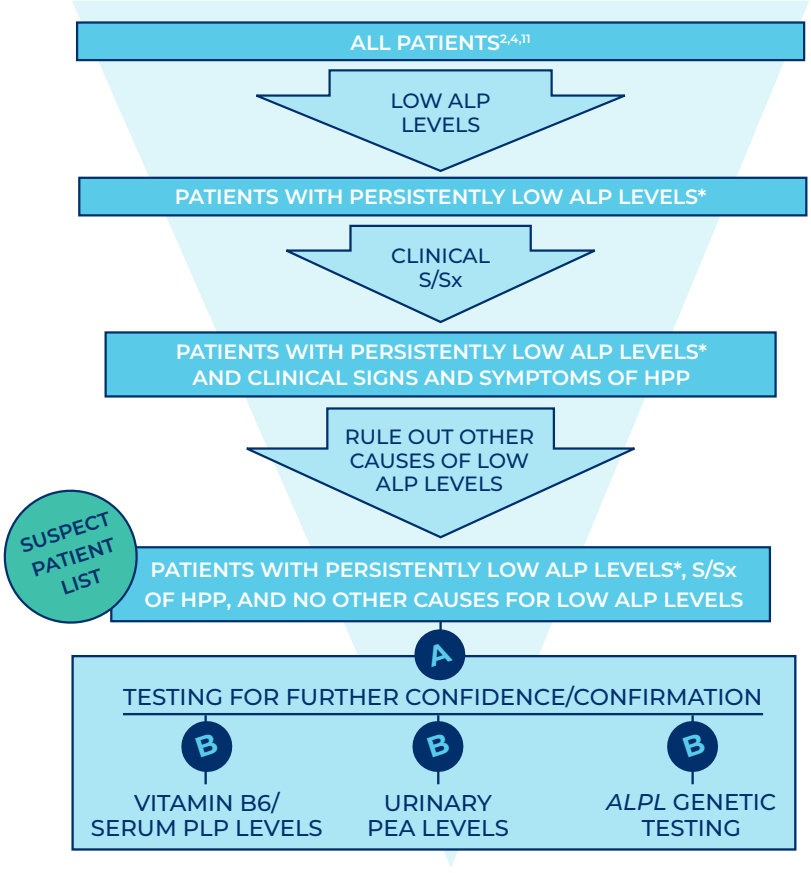
When vitamin B6/serum PLP and urinary PEA lab tests are ordered and suspect patient criteria are met, a BPA can be used to signal reminders to the HCP collecting the specimens on how to obtain optimum sampling.[2,3] For example:

- Vitamin B6/serum PLP sample is light sensitive and can cause inactivation of enzymes in certain light conditions. Refer to your lab specialist for specimen collection requirements[17]
- PEA levels are assessed by collecting a urine sample; however, the preferred method of collection varies (eg, spot vs 24-hour urine sample).[7,13] Please consult with the specific laboratory to discuss sample type, duration and timing of collection, as urinary protein levels can vary throughout a 24-hour period[13]

B BPAs for genetic testing

The HCP may elect to obtain genetic testing to look for mutations in the *ALPL* gene. A BPA can be used to provide education. For example:

- The *ALPL* gene is responsible for encoding the ALP enzyme. Mutations in the *ALPL* gene cause low ALP enzyme activity[5]
- Although genetic testing of the *ALPL* gene is not required for an HPP diagnosis, it may be useful for genetic counseling purposes[15]
- If the genetic test is negative or inconclusive, the diagnosis of HPP is not necessarily excluded; the test result may arise from mutations of unknown significance or mutations that are undetectable because they lie in intronic or regulatory sequences for other genes[18]



All additional diagnostic follow-up must be medically appropriate and determined by the individual decision of the treating HCP.

*Refer to your lab for appropriate age- and sex-adjusted reference range.

4

EHR build considerations

There are subtle differences between the various EHR systems. Each has similar functionality, but there may be differences in the naming conventions of EHR system features. Some naming conventions are outlined in this section.

The toolkit is provided for informational purposes only and does not substitute the internal review of your institution. Please coordinate with your institution's approval process before implementing an EHR build.

4. Available tools in the EHR for providers

- Generating and maintaining suspect patient lists empowers organizations to surface patients who meet certain clinical and demographic criteria. These may also be named "worklists" depending on the system[19,20]
- BPAs allow organizations to notify providers when certain clinical activities should be prioritized for a particular patient. This functionality can account for a variety of clinical variables throughout the patient journey and may also be named "discern alerts"[21-23]
- Standardized order sets allow providers to easily understand and order the most relevant tests and treatment options for patients who meet certain disease criteria or are being seen in a particular department. These may also be known as "power plans" depending on the system[24,25]
- EHR systems have patient portals that allow patients to stay in touch with their care teams, review their schedules, access personalized patient educational materials, and be more involved in managing their health
  - » **Epic MyChart** (https://www.epic.com/software#PatientEngagement)
  - » **Cerner® HealtheLife℠** (https://www.cerner.com/solutions/patient-engagement#:~:text=The%20Cerner%20patient%20portal%20offering,people%20proactively%20manage%20their%20health)
  - » **Meditech Health Portal** (https://ehr.meditech.com/ehr-solutions/patient-engagement)
  - » **Allscripts® FollowMyHealth®** (https://www.allscripts.com/solution/patient-engagement-followmyhealth)

Patient communication considerations

Follow established communication protocols, especially those related to communicating sensitive information to patients.

- You may wish to notify patients to contact their HCP and schedule a follow-up appointment

The patient list and BPA functionality already exist in many EHR systems. Alexion did not sponsor, design, create, or otherwise modify this functionality in any manner. The instructions have not been designed to and are not tools and/or solutions for meeting Meaningful Use, Advancing Care information, and/or any other quality/accreditation requirement.

Implementing, monitoring, and maintaining the program

5

To assess the program, including surfaced suspect patients, you will need to monitor it on an ongoing basis. Remember, it will be essential to be clear about what you want to achieve and how you will measure it.[26]

5. Implementing, monitoring, and maintaining the program

Step 1: Establish a Clinical Champion

- The Clinical Champion can help communicate the value of the program and act as a resource during the planning process
- It's important to establish a Clinical Champion for the project (a medical specialist with expertise in HPP) who can answer questions and help direct and oversee successful program implementation
- The Clinical Champion can provide ongoing support, including monitoring the program and assisting providers with challenging cases

Step 2: Identify, engage, and communicate with stakeholders[26,27]

- Identify and collaborate with relevant stakeholders within your health systems (including specialists) who may see undiagnosed HPP patients.* The most common specialists include the following[11]: (also see Appendix A for complete list)
  - » Endocrinologists
  - » Orthopedists
  - » Physical therapists/occupational therapists
  - » Rheumatologists
  - » Immunologists
  - » Pulmonologists
  - » Intensivists
  - » Pediatricians
  - » Neonatologists
  - » Neurologists
  - » Nursing
  - » Specialty nursing
  - » Nephrologists
  - » Geneticists/genetics counselors
  - » Pain management specialists

*Please see Appendix for full listing of possible specialists.

Learn, understand, and comply with your institution's requirements for implementing.

Step 3: Develop and execute the implementation plan

- Utilize the clinical criteria for HPP
- It's important to note differences between inpatient and outpatient care when implementing the program
- Leverage the recommended codes in Appendix B to create suspect patient lists
- Consider implementation of BPAs (See page 6 for more details)
- Provide HPP education and resources within the clinical alert using web links, such as: https://rarediseases.info.nih.gov/diseases/6734/hypophosphatasia or https://rarediseases.org/rare-diseases/hypophosphatasia/
- Remind HCPs to follow process of communication to departments that will be affected

Step 4: Develop measures[26-28]

Determine metrics for success. For example:

- Amount of time from suspect patient alert or on a report to the HCP for evaluation to rule in or rule out HPP
- Number of patients for which an alert helps the HCP to confirm or rule out an HPP diagnosis for a suspect patient

Step 5: Develop a monitoring and evaluation framework[26]

- The Clinical Champion can monitor and evaluate suspect HPP patient lists on a routine (eg, monthly, bimonthly) basis to help the patient's provider rule in or rule out HPP
- The Clinical Champion can monitor and evaluate the BPA program as determined by the project team or institutional guidance

Step 6: Ongoing improvement[26]

- Assess HPP diagnostic criteria to ensure that they are current
  - » Determine the appropriate timeframe for reassessment based on institutional standards (eg, annually)
  - » Check deciphEHRrare.com for updates
- Evaluate the effectiveness of HPP suspect patient lists and BPAs to triage suspect patients to confirm or rule out HPP

Appendix A— HCP specialist list[5]

Identify and collaborate with relevant stakeholders within your health systems (including specialists) who may see undiagnosed HPP patients. See the list of possible specialists below. Learn, understand, and comply with your institution's requirements for implementing.

- Endocrinologists
- Orthopedists
- Geneticists/genetic counselors
- Nursing
- Physical therapists/occupational therapists
- Psychiatrists
- Immunologists
- Rheumatologists
- Radiologists
- Pain specialists
- Gastrointestinal specialists
- Nutritionists/dietitians
- Nephrologists
- Social workers
- Ophthalmologists
- Dentists
- Neonatologists
- Pulmonologists
- Pediatricians
- Neurosurgeons
- Neurologists
- ENTs
- Intensivists
- Neuropsychologists
- Specialty nursing

ENT=ear, nose, and throat.

Appendix B— Code list instructions

The clinical criteria for HPP that are required for a patient to appear on the suspect patient list are consistent across all age groups. However, clinical signs and symptoms of HPP may present differently depending on the patient's age.

The medical codes that represent these criteria are found here in the appendix.

Clinical Criteria for HPP	Overview of Code Sets for Each Clinical Criteria/Age Group
1. Persistently low age- and sex-adjusted ALP enzyme levels	**Code set to facilitate identifying persistently low ALP levels is consistent and should be used across all age groups** *Important Note*: Additional steps are necessary to determine persistently low values. The codes can be used to identify patients with ALP results. Low values can be informed by the processing lab's reference ranges and/or low result flag.
2. Signs and symptoms of HPP	**Code set is specific to age group** Diagnostic criteria are consistent across groups. However, key differences in Clinical Signs and Symptoms exist for perinatal, infantile, childhood, and adult HPP as outlined in *Section 1, Diagnostic Criteria and Investigation of Clinical Signs and Symptoms*. See specific signs and symptoms code set in this appendix for each of the following age groups: • **Adult HPP (≥18 years) signs and symptoms** • **Childhood HPP (≥6 months to <18 years) signs and symptoms** • **Infantile HPP (birth to <6 months) signs and symptoms** • **Perinatal HPP (*in utero* or at birth) signs and symptoms**
3. Rule out other causes of low ALP levels	**Code set to rule out other causes of low ALP levels is consistent and should be used across all age groups**

- All codes are listed at the parent level. Determining level of specificity (eg, specific codes within parent trees) is at the discretion of the institution
- Codes may change over time; updates will be maintained at deciphEHRrare.com
- An Excel spreadsheet version is also available on the webpage for your convenience
- The institution is responsible for selection of codes based on the specific situation and patient needs

Appendix B— Codes to facilitate persistently low ALP results

Common to all age groups

A suspect patient list begins with persistently low (2 or more within 6 months) ALP levels in the laboratory results section. ALP levels can be captured in the EHR by utilizing LOINC codes to retrieve the patient's lab test result values.

IMPORTANT: Additional steps are necessary to determine low ALP levels. Once LOINC codes have returned numerical values for ALP lab tests, the EHR must set parameters for what constitutes high or low values. These parameters can be informed by the institution's processing lab reference ranges and/or institutional policies.

Category	Inclusion/ Exclusion Flag	Alexion Rule	Code Type	Code	Code Description
ALP Test	Inclusion	Alkaline phosphatase (ALP) test*	LOINC	24332-9	Alkaline phosphatase isoenz panel - serum or plasma
ALP Test	Inclusion	Alkaline phosphatase (ALP) test*	LOINC	24322-0	Comprehensive metabolic 1998 panel - serum or plasma
ALP Test	Inclusion	Alkaline phosphatase (ALP) test*	LOINC	24323-8	Comprehensive metabolic 2000 panel - serum or plasma
ALP Test	Inclusion	Alkaline phosphatase (ALP) test*	LOINC	24324-6	Hepatic function 1996 panel - serum or plasma
ALP Test	Inclusion	Alkaline phosphatase (ALP) test*	LOINC	24325-3	Hepatic function 2000 panel - serum or plasma

*While LOINC codes will provide the values of test results, it will be at the discretion of each system to define and set low values. These can be informed by the processing lab's reference ranges, low result flags, and/or clinical guidelines.

Appendix B— Codes for adult HPP signs and symptoms

6

Note: Pediatric signs and symptoms may also appear in adult patient medical histories; codes for these are included in the below on pages 14-16.

Category	Inclusion/ Exclusion Flag	Alexion Rule	Code Type	Code	Code Description
Adult					
Adult Clinical Signs and Symptoms	Inclusion	CPPD (calcium pyrophosphate deposition disease [pseudogout])	ICD-10	M11.2	Other chondrocalcinosis, not otherwise specified
Adult Clinical Signs and Symptoms	Inclusion	CPPD (calcium pyrophosphate deposition disease [pseudogout])	SNOMED-CT	239832006	Calcium pyrophosphate deposition disease (disorder)
Adult Clinical Signs and Symptoms	Inclusion	Craniosynostosis	ICD-10	Q75.0	Craniosynostosis
Adult Clinical Signs and Symptoms	Inclusion	Craniosynostosis	SNOMED-CT	57219006	Craniosynostosis syndrome (disorder)
Adult Clinical Signs and Symptoms	Inclusion	Delayed walking, waddling gait, delayed/missed motor milestones, and failure to thrive	ICD-10	R62.0	Delayed milestone
Adult Clinical Signs and Symptoms	Inclusion	Delayed walking, waddling gait, delayed/missed motor milestones, and failure to thrive	ICD-10	R26.2	Difficulty in walking, not elsewhere classified
Adult Clinical Signs and Symptoms	Inclusion	Delayed walking, waddling gait, delayed/missed motor milestones, and failure to thrive	ICD-10	R26.8	Other and unspecified abnormalities of gait and mobility
Adult Clinical Signs and Symptoms	Inclusion	Delayed walking, waddling gait, delayed/missed motor milestones, and failure to thrive	ICD-10	R26.9	Gait abnormality
Adult Clinical Signs and Symptoms	Inclusion	Delayed walking, waddling gait, delayed/missed motor milestones, and failure to thrive	ICD-10	R62.51	Failure to thrive (child over 28 days old)
Adult Clinical Signs and Symptoms	Inclusion	Delayed walking, waddling gait, delayed/missed motor milestones, and failure to thrive	SNOMED-CT	307653008	Clumsiness - motor delay (disorder)
Adult Clinical Signs and Symptoms	Inclusion	Delayed walking, waddling gait, delayed/missed motor milestones, and failure to thrive	SNOMED-CT	703477003	Developmental delay in fine motor function (disorder)
Adult Clinical Signs and Symptoms	Inclusion	Delayed walking, waddling gait, delayed/missed motor milestones, and failure to thrive	SNOMED-CT	271706000	Waddling gait (finding)
Adult Clinical Signs and Symptoms	Inclusion	Delayed walking, waddling gait, delayed/missed motor milestones, and failure to thrive	SNOMED-CT	430099007	Gross motor development delay (disorder)

Category	Inclusion/ Exclusion Flag	Alexion Rule	Code Type	Code	Code Description
Adult Clinical Signs and Symptoms	Inclusion	Delayed walking, waddling gait, delayed/missed motor milestones, and failure to thrive	SNOMED-CT	54840006	Failure to thrive (disorder)
Adult Clinical Signs and Symptoms	Inclusion	Loss of periodontal tissue	ICD-10	K08.0	Exfoliation of teeth due to systemic causes
Adult Clinical Signs and Symptoms	Inclusion	Loss of periodontal tissue	ICD-10	K08.129	Complete loss of teeth due to periodontal diseases
Adult Clinical Signs and Symptoms	Inclusion	Loss of periodontal tissue	ICD-10	K08.429	Partial loss of teeth due to periodontal diseases
Adult Clinical Signs and Symptoms	Inclusion	Loss of periodontal tissue	ICD-10	K08.9	Disorder of teeth and supporting structures, unspecified
Adult Clinical Signs and Symptoms	Inclusion	Loss of periodontal tissue	SNOMED-CT	25540007	Tooth loss (finding)
Adult Clinical Signs and Symptoms	Inclusion	Ectopic calcification	SNOMED-CT	237896000	Extraskeletal calcification (disorder)
Adult Clinical Signs and Symptoms	Inclusion	Ectopic calcification	SNOMED-CT	44551007	Muscular ossification (disorder)
Adult Clinical Signs and Symptoms	Inclusion	Ectopic calcification	ICD-10	M61	Calcification and ossification of muscle
Adult Clinical Signs and Symptoms	Inclusion	Fatigue	ICD-10	R53	Malaise and fatigue
Adult Clinical Signs and Symptoms	Inclusion	Fatigue	SNOMED-CT	84229001	Fatigue (finding)
Adult Clinical Signs and Symptoms	Inclusion	Fractures (low trauma fractures, delayed healing or recurrent fractures, pseudofractures, and metatarsal stress fractures)	ICD-10	M84.7	Nontraumatic fracture, not elsewhere classified
Adult Clinical Signs and Symptoms	Inclusion	Fractures (low trauma fractures, delayed healing or recurrent fractures, pseudofractures, and metatarsal stress fractures)	SNOMED-CT	125605004	Fracture of bone (disorder)
Adult Clinical Signs and Symptoms	Inclusion	Gait disturbance	ICD-10	R26	Abnormalities of gait and mobility
Adult Clinical Signs and Symptoms	Inclusion	Gait disturbance	SNOMED-CT	22325002	Abnormal gait (finding)
Adult Clinical Signs and Symptoms	Inclusion	History of rickets	ICD-10	E64.3	Sequelae of rickets
Adult Clinical Signs and Symptoms	Inclusion	History of rickets	ICD-10	E83.32	Hereditary vitamin D-dependent rickets (type 1) (type 2)
Adult Clinical Signs and Symptoms	Inclusion	History of rickets	SNOMED-CT	41345002	Rickets (disorder)
Adult Clinical Signs and Symptoms	Inclusion	Hypercalcemia/hypercalciuria	SNOMED-CT	66931009	Hypercalcemia (disorder)
Adult Clinical Signs and Symptoms	Inclusion	Hypercalcemia/hypercalciuria	SNOMED-CT	71938000	Hypercalciuria (disorder)
Adult Clinical Signs and Symptoms	Inclusion	Hypercalcemia/hypercalciuria	ICD-10	E83.52	Hypercalcemia
Adult Clinical Signs and Symptoms	Inclusion	Hypercalcemia/hypercalciuria	ICD-10	R82.994	Hypercalciuria
Adult Clinical Signs and Symptoms	Inclusion	Impaired mobility	ICD-10	Z74. 09	Reduced mobility
Adult Clinical Signs and Symptoms	Inclusion	Impaired mobility	SNOMED-CT	82971005	Impaired mobility (finding)
Adult Clinical Signs and Symptoms	Inclusion	Joint hypermobility	ICD-10	M35.7	Hypermobility syndrome
Adult Clinical Signs and Symptoms	Inclusion	Joint hypermobility	SNOMED-CT	298181000	Range of joint movement increased (finding)
Adult Clinical Signs and Symptoms	Inclusion	Muscle weakness	ICD-10	M62.81	Muscle weakness (generalized)

Category	Inclusion/ Exclusion Flag	Alexion Rule	Code Type	Code	Code Description
Adult Clinical Signs and Symptoms	Inclusion	Muscle weakness	SNOMED-CT	26544005	Muscle weakness (finding)
Adult Clinical Signs and Symptoms	Inclusion	Nephrocalcinosis	ICD-10	E83.59	Nephrocalcinosis
Adult Clinical Signs and Symptoms	Inclusion	Nephrocalcinosis	SNOMED-CT	48638002	Nephrocalcinosis (disorder)
Adult Clinical Signs and Symptoms	Inclusion	Ophthalmic calcifications	ICD-10	H18.0	Corneal pigmentations and deposits
Adult Clinical Signs and Symptoms	Inclusion	Ophthalmic calcifications	ICD-10	H11.11	Conjunctival deposits
Adult Clinical Signs and Symptoms	Inclusion	Ophthalmic calcifications	SNOMED-CT	62660000	Conjunctival deposit (disorder)
Adult Clinical Signs and Symptoms	Inclusion	Ophthalmic calcifications	SNOMED-CT	74460005	Corneal deposit (disorder)
Adult Clinical Signs and Symptoms	Inclusion	Osteomalacia	ICD-10	M83	Adult osteomalacia
Adult Clinical Signs and Symptoms	Inclusion	Osteomalacia	SNOMED-CT	4598005	Osteomalacia (disorder)
Adult Clinical Signs and Symptoms	Inclusion	Pain (bone, muscle, and/or joint)	ICD-10	M85.8	Other specified disorders of bone density and structure
Adult Clinical Signs and Symptoms	Inclusion	Pain (bone, muscle, and/or joint)	ICD-10	M25.5	Pain in joint
Adult Clinical Signs and Symptoms	Inclusion	Pain (bone, muscle, and/or joint)	ICD-10	M79.1	Myalgia
Adult Clinical Signs and Symptoms	Inclusion	Pain (bone, muscle, and/or joint)	SNOMED-CT	12584003	Bone pain (finding)
Adult Clinical Signs and Symptoms	Inclusion	Pain (bone, muscle, and/or joint)	SNOMED-CT	68962001	Muscle pain (finding)
Adult Clinical Signs and Symptoms	Inclusion	Pain (bone, muscle, and/or joint)	SNOMED-CT	57676002	Joint pain (finding)
Adult Clinical Signs and Symptoms	Inclusion	Premature tooth loss	ICD-10	K00.6	Disturbances in tooth eruption
Adult Clinical Signs and Symptoms	Inclusion	Premature tooth loss	SNOMED-CT	42756003	Premature tooth loss (finding)
Adult Clinical Signs and Symptoms	Inclusion	Short stature	ICD-10	R62.8	Other lack of expected normal physiological development
Adult Clinical Signs and Symptoms	Inclusion	Short stature	SNOMED-CT	237836003	Short stature disorder (disorder)
Adult Clinical Signs and Symptoms	Inclusion	Skeletal deformities	ICD-10	Q79.9	Congenital malformation of musculoskeletal system, unspecified
Adult Clinical Signs and Symptoms	Inclusion	Skeletal deformities	ICD-10	Q79.8	Other congenital malformations of musculoskeletal system
Adult Clinical Signs and Symptoms	Inclusion	Skeletal deformities	ICD-10	M41	Scoliosis

Appendix B— Codes for childhood HPP signs and symptoms

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Category	Inclusion/ Exclusion Flag	Alexion Rule	Code Type	Code	Code Description
Childhood					
Childhood Clinical Signs and Symptoms	Inclusion	Loss of periodontal tissue	ICD-10	K08.0	Exfoliation of teeth due to systemic causes
Childhood Clinical Signs and Symptoms	Inclusion	Loss of periodontal tissue	ICD-10	K08.129	Complete loss of teeth due to periodontal diseases
Childhood Clinical Signs and Symptoms	Inclusion	Loss of periodontal tissue	ICD-10	K08.429	Partial loss of teeth due to periodontal diseases
Childhood Clinical Signs and Symptoms	Inclusion	Loss of periodontal tissue	ICD-10	K08.9	Disorder of teeth and supporting structures, unspecified
Childhood Clinical Signs and Symptoms	Inclusion	Loss of periodontal tissue	SNOMED-CT	25540007	Tooth loss (finding)
Childhood Clinical Signs and Symptoms	Inclusion	Fractures (low trauma fractures, delayed healing or recurrent fractures, pseudofractures, and metatarsal stress fractures)	ICD-10	M84.7	Nontraumatic fracture, not elsewhere classified
Childhood Clinical Signs and Symptoms	Inclusion	Fractures (low trauma fractures, delayed healing or recurrent fractures, pseudofractures, and metatarsal stress fractures)	SNOMED-CT	125605004	Fracture of bone (disorder)
Childhood Clinical Signs and Symptoms	Inclusion	Delayed walking, waddling gait, delayed/missed motor milestones, and failure to thrive	ICD-10	R62.0	Delayed milestone
Childhood Clinical Signs and Symptoms	Inclusion	Delayed walking, waddling gait, delayed/missed motor milestones, and failure to thrive	SNOMED-CT	703477003	Developmental delay in fine motor function (disorder)
Childhood Clinical Signs and Symptoms	Inclusion	Delayed walking, waddling gait, delayed/missed motor milestones, and failure to thrive	ICD-10	R26.2	Difficulty in walking, not elsewhere classified
Childhood Clinical Signs and Symptoms	Inclusion	Delayed walking, waddling gait, delayed/missed motor milestones, and failure to thrive	ICD-10	R26.8	Other and unspecified abnormalities of gait and mobility
Childhood Clinical Signs and Symptoms	Inclusion	Delayed walking, waddling gait, delayed/missed motor milestones, and failure to thrive	ICD-10	R26.9	Gait abnormality
Childhood Clinical Signs and Symptoms	Inclusion	Delayed walking, waddling gait, delayed/missed motor milestones, and failure to thrive	SNOMED-CT	307653008	Clumsiness - motor delay (disorder)
Childhood Clinical Signs and Symptoms	Inclusion	Delayed walking, waddling gait, delayed/missed motor milestones, and failure to thrive	SNOMED-CT	271706000	Waddling gait (finding)

Category	Inclusion/ Exclusion Flag	Alexion Rule	Code Type	Code	Code Description
Childhood Clinical Signs and Symptoms	Inclusion	Bowing deformities with or without fractures	ICD-10	Q68.4	Congenital bowing of tibia and fibula
Childhood Clinical Signs and Symptoms	Inclusion	Bowing deformities with or without fractures	ICD-10	Q68.3	Congenital bowing of femur
Childhood Clinical Signs and Symptoms	Inclusion	Bowing deformities with or without fractures	ICD-10	Q68.5	Congenital bowing of long bones of leg, unspecified
Childhood Clinical Signs and Symptoms	Inclusion	Bowing deformities with or without fractures	SNOMED-CT	716098006	Congenital bowing of long bone (disorder)
Childhood Clinical Signs and Symptoms	Inclusion	Bowing deformities with or without fractures	SNOMED-CT	298360005	Bowing deformity of bone (finding)
Childhood Clinical Signs and Symptoms	Inclusion	Craniosynostosis	ICD-10	Q75.0	Craniosynostosis
Childhood Clinical Signs and Symptoms	Inclusion	Craniosynostosis	SNOMED-CT	57219006	Craniosynostosis syndrome (disorder)
Childhood Clinical Signs and Symptoms	Inclusion	Short stature	ICD-10	R62.8	Other lack of expected normal physiological development
Childhood Clinical Signs and Symptoms	Inclusion	Short stature	SNOMED-CT	237836003	Short stature disorder (disorder)
Childhood Clinical Signs and Symptoms	Inclusion	Joint hypermobility	ICD-10	M35.7	Hypermobility syndrome
Childhood Clinical Signs and Symptoms	Inclusion	Joint hypermobility	SNOMED-CT	298181000	Range of joint movement increased (finding)
Childhood Clinical Signs and Symptoms	Inclusion	Muscle weakness	ICD-10	M62.81	Muscle weakness (generalized)
Childhood Clinical Signs and Symptoms	Inclusion	Muscle weakness	SNOMED-CT	26544005	Muscle weakness (finding)
Childhood Clinical Signs and Symptoms	Inclusion	Pain (bone, muscle, and/or joint)	ICD-10	M85.8	Other specified disorders of bone density and structure
Childhood Clinical Signs and Symptoms	Inclusion	Pain (bone, muscle, and/or joint)	ICD-10	M25.5	Pain in joint
Childhood Clinical Signs and Symptoms	Inclusion	Pain (bone, muscle, and/or joint)	ICD-10	M79.1	Myalgia
Childhood Clinical Signs and Symptoms	Inclusion	Pain (bone, muscle, and/or joint)	SNOMED-CT	12584003	Bone pain (finding)
Childhood Clinical Signs and Symptoms	Inclusion	Pain (bone, muscle, and/or joint)	SNOMED-CT	68962001	Muscle pain (finding)
Childhood Clinical Signs and Symptoms	Inclusion	Pain (bone, muscle, and/or joint)	SNOMED-CT	57676002	Joint pain (finding)
Childhood Clinical Signs and Symptoms	Inclusion	Hypercalcemia/hypercalciuria	SNOMED-CT	71938000	Hypercalciuria (disorder)
Childhood Clinical Signs and Symptoms	Inclusion	Hypercalcemia/hypercalciuria	ICD-10	R82.994	Hypercalciuria
Childhood Clinical Signs and Symptoms	Inclusion	Hypercalcemia/hypercalciuria	SNOMED-CT	66931009	Hypercalcemia (disorder)
Childhood Clinical Signs and Symptoms	Inclusion	Hypercalcemia/hypercalciuria	ICD-10	E83.52	Hypercalcemia
Childhood Clinical Signs and Symptoms	Inclusion	Nephrocalcinosis	ICD-10	E83.59	Nephrocalcinosis
Childhood Clinical Signs and Symptoms	Inclusion	Nephrocalcinosis	SNOMED-CT	48638002	Nephrocalcinosis (disorder)
Childhood Clinical Signs and Symptoms	Inclusion	Ophthalmic calcifications	ICD-10	H18.0	Corneal pigmentations and deposits
Childhood Clinical Signs and Symptoms	Inclusion	Ophthalmic calcifications	ICD-10	H11.11	Conjunctival deposits
Childhood Clinical Signs and Symptoms	Inclusion	Ophthalmic calcifications	SNOMED-CT	62660000	Conjunctival deposit (disorder)
Childhood Clinical Signs and Symptoms	Inclusion	Ophthalmic calcifications	SNOMED-CT	74460005	Corneal deposit (disorder)

Category	Inclusion/ Exclusion Flag	Alexion Rule	Code Type	Code	Code Description
Childhood Clinical Signs and Symptoms	Inclusion	Poor bone mineralization	ICD-10	E83.3	Disorders of phosphorus metabolism and phosphatases
Childhood Clinical Signs and Symptoms	Inclusion	Poor bone mineralization	ICD-10	E55.0	Rickets, active
Childhood Clinical Signs and Symptoms	Inclusion	Poor bone mineralization	SNOMED-CT	126533001	Disorder with defective osteoid mineralization (disorder)
Childhood Clinical Signs and Symptoms	Inclusion	Poor bone mineralization	SNOMED-CT	391032006	X-ray evidence of poor mineralization (finding)
Childhood Clinical Signs and Symptoms	Inclusion	Chest deformity (rachitic-like lesions, gracile ribs, rib fractures)	ICD-10	S22.3	Fracture of one rib
Childhood Clinical Signs and Symptoms	Inclusion	Chest deformity (rachitic-like lesions, gracile ribs, rib fractures)	ICD-10	S22.4	Multiple fractures of ribs
Childhood Clinical Signs and Symptoms	Inclusion	Chest deformity (rachitic-like lesions, gracile ribs, rib fractures)	ICD-10	Q67.8	Other congenital deformities of chest
Childhood Clinical Signs and Symptoms	Inclusion	Chest deformity (rachitic-like lesions, gracile ribs, rib fractures)	ICD-10	M84.9	Disorder of continuity of bone, unspecified
Childhood Clinical Signs and Symptoms	Inclusion	Chest deformity (rachitic-like lesions, gracile ribs, rib fractures)	ICD-10	M84.8	Other disorders of continuity of bone
Childhood Clinical Signs and Symptoms	Inclusion	Chest deformity (rachitic-like lesions, gracile ribs, rib fractures)	SNOMED-CT	448488004	Deformity of chest wall (disorder)
Childhood Clinical Signs and Symptoms	Inclusion	Chest deformity (rachitic-like lesions, gracile ribs, rib fractures)	SNOMED-CT	298735007	Deformity of rib (disorder)
Childhood Clinical Signs and Symptoms	Inclusion	Chest deformity (rachitic-like lesions, gracile ribs, rib fractures)	SNOMED-CT	33737001	Fracture of rib (disorder)

Appendix B— Codes for infantile HPP signs and symptoms

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Category	Inclusion/ Exclusion Flag	Alexion Rule	Code Type	Code	Code Description
Infantile					
Infantile Clinical Signs and Symptoms	Inclusion	Premature deciduous tooth loss	ICD-10	K08.129	Complete loss of teeth
Infantile Clinical Signs and Symptoms	Inclusion	Premature deciduous tooth loss	ICD-10	K08.429	Partial loss of teeth
Infantile Clinical Signs and Symptoms	Inclusion	Premature deciduous tooth loss	ICD-10	K08.9	Disorder of teeth and supporting structures, unspecified
Infantile Clinical Signs and Symptoms	Inclusion	Premature deciduous tooth loss	SNOMED-CT	25540007	Tooth loss (finding)
Infantile Clinical Signs and Symptoms	Inclusion	Bowing deformities with or without fractures	ICD-10	Q68.4	Congenital bowing of tibia and fibula
Infantile Clinical Signs and Symptoms	Inclusion	Bowing deformities with or without fractures	ICD-10	Q68.3	Congenital bowing of femur
Infantile Clinical Signs and Symptoms	Inclusion	Bowing deformities with or without fractures	ICD-10	Q68.5	Congenital bowing of long bones of leg, unspecified
Infantile Clinical Signs and Symptoms	Inclusion	Bowing deformities with or without fractures	SNOMED-CT	716098006	Congenital bowing of long bone (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Bowing deformities with or without fractures	SNOMED-CT	298360005	Bowing deformity of bone (finding)
Infantile Clinical Signs and Symptoms	Inclusion	Limb shortening	ICD-10	Q71	Reduction defects of upper limb
Infantile Clinical Signs and Symptoms	Inclusion	Limb shortening	ICD-10	Q72	Reduction defects of lower limb
Infantile Clinical Signs and Symptoms	Inclusion	Limb shortening	ICD-10	Q73	Reduction defects of unspecified limb
Infantile Clinical Signs and Symptoms	Inclusion	Limb shortening	SNOMED-CT	67341007	Longitudinal deficiency of limb (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Craniosynostosis leading to raised intracranial pressure	ICD-10	Q75.0	Craniosynostosis
Infantile Clinical Signs and Symptoms	Inclusion	Craniosynostosis leading to raised intracranial pressure	SNOMED-CT	57219006	Craniosynostosis syndrome (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Muscle weakness with hypotonia	ICD-10	M62.81	Muscle weakness (generalized)
Infantile Clinical Signs and Symptoms	Inclusion	Muscle weakness with hypotonia	SNOMED-CT	26544005	Muscle weakness (finding)
Infantile Clinical Signs and Symptoms	Inclusion	Muscle weakness with hypotonia	SNOMED-CT	398152000	Poor muscle tone (finding)
Infantile Clinical Signs and Symptoms	Inclusion	Hypercalciuria/hypercalcemia	SNOMED-CT	71938000	Hypercalciuria (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Hypercalciuria/hypercalcemia	ICD-10	R82.994	Hypercalciuria

Category	Inclusion/ Exclusion Flag	Alexion Rule	Code Type	Code	Code Description
Infantile Clinical Signs and Symptoms	Inclusion	Hypercalciuria/hypercalcemia	ICD-10	E83.52	Hypercalcemia
Infantile Clinical Signs and Symptoms	Inclusion	Hypercalciuria/hypercalcemia	SNOMED-CT	66931009	Hypercalcemia (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Nephrocalcinosis	ICD-10	E83.59	Nephrocalcinosis
Infantile Clinical Signs and Symptoms	Inclusion	Nephrocalcinosis	ICD-10	N29.8	Other disorders of kidney and ureter in other diseases classified elsewhere
Infantile Clinical Signs and Symptoms	Inclusion	Nephrocalcinosis	SNOMED-CT	48638002	Nephrocalcinosis (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Ophthalmic calcifications	ICD-10	H18.0	Corneal pigmentations and deposits
Infantile Clinical Signs and Symptoms	Inclusion	Ophthalmic calcifications	ICD-10	H11.11	Conjunctival deposits
Infantile Clinical Signs and Symptoms	Inclusion	Ophthalmic calcifications	SNOMED-CT	62660000	Conjunctival deposit (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Ophthalmic calcifications	SNOMED-CT	74460005	Corneal deposit (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Severe skeletal hypomineralization or undermineralization	ICD-10	E83.3	Disorders of phosphorus metabolism and phosphatases
Infantile Clinical Signs and Symptoms	Inclusion	Severe skeletal hypomineralization or undermineralization	ICD-10	E55.0	Rickets, active
Infantile Clinical Signs and Symptoms	Inclusion	Severe skeletal hypomineralization or undermineralization	SNOMED-CT	126533001	Disorder with defective osteoid mineralization (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Severe skeletal hypomineralization or undermineralization	SNOMED-CT	391032006	X-ray evidence of poor mineralization (finding)
Infantile Clinical Signs and Symptoms	Inclusion	Severe chest deformity (rachitic chest, gracile ribs, rib fractures, narrow thoracic inlet)	ICD-10	S22.3	Fracture of rib
Infantile Clinical Signs and Symptoms	Inclusion	Severe chest deformity (rachitic chest, gracile ribs, rib fractures, narrow thoracic inlet)	ICD-10	S22.4	Multiple fractures of ribs
Infantile Clinical Signs and Symptoms	Inclusion	Severe chest deformity (rachitic chest, gracile ribs, rib fractures, narrow thoracic inlet)	SNOMED-CT	33737001	Fracture of rib (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Metaphyseal radiolucencies	SNOMED-CT	128310007	Decreased radiologic density (finding)
Infantile Clinical Signs and Symptoms	Inclusion	Hearing loss	ICD-10	H91.9	Hearing loss, unspecified
Infantile Clinical Signs and Symptoms	Inclusion	Hearing loss	ICD-10	H91.8	Other specified hearing loss
Infantile Clinical Signs and Symptoms	Inclusion	Hearing loss	ICD-10	H91.2	Sudden idiopathic hearing loss
Infantile Clinical Signs and Symptoms	Inclusion	Hearing loss	ICD-10	H90	Conductive and sensorineural hearing loss
Infantile Clinical Signs and Symptoms	Inclusion	Hearing loss	SNOMED-CT	15188001	Hearing loss (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Gastrointestinal dysfunctions (reflux/emesis)	ICD-10	K21	Gastro-oesophageal reflux disease
Infantile Clinical Signs and Symptoms	Inclusion	Gastrointestinal dysfunctions (reflux/emesis)	ICD-10	R11	Nausea and vomiting
Infantile Clinical Signs and Symptoms	Inclusion	Gastrointestinal dysfunctions (reflux/emesis)	SNOMED-CT	10999201000-119100	Gastroesophageal reflux in child (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Gastrointestinal dysfunctions (reflux/emesis)	SNOMED-CT	422400008	Vomiting (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Respiratory failure or insufficiency requiring support	ICD-10	R06.89	Respiratory insufficiency

Category	Inclusion/ Exclusion Flag	Alexion Rule	Code Type	Code	Code Description
Infantile Clinical Signs and Symptoms	Inclusion	Respiratory failure or insufficiency requiring support	ICD-10	J96	Respiratory failure, not elsewhere classified
Infantile Clinical Signs and Symptoms	Inclusion	Respiratory failure or insufficiency requiring support	ICD-10	P22	Respiratory distress of newborn
Infantile Clinical Signs and Symptoms	Inclusion	Respiratory failure or insufficiency requiring support	SNOMED-CT	409622000	Respiratory failure (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Seizures (vitamin B6 dependent)	ICD-10	P91.9	Disturbance of cerebral status of newborn, unspecified
Infantile Clinical Signs and Symptoms	Inclusion	Seizures (vitamin B6 dependent)	ICD-10	R56.8	Other and unspecified convulsions
Infantile Clinical Signs and Symptoms	Inclusion	Seizures (vitamin B6 dependent)	SNOMED-CT	734434007	Pyridoxine-dependent epilepsy (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Underossification of cranial vault	SNOMED-CT	253980008	Defect of skull ossification (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Underossification of cranial vault	ICD-10	Q75.9	Congenital malformation of skull and face bones, unspecified
Infantile Clinical Signs and Symptoms	Inclusion	Underossification of cranial vault	ICD-10	Q75.8	Other specified congenital malformations of skull and face bones
Infantile Clinical Signs and Symptoms	Inclusion	High-pitched crying related to laryngeal hypotonia	ICD-10	Q31.5	Congenital laryngomalacia
Infantile Clinical Signs and Symptoms	Inclusion	High-pitched crying related to laryngeal hypotonia	SNOMED-CT	333100011-9108	Laryngeal dystonia (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	High-pitched crying related to laryngeal hypotonia	SNOMED-CT	38086007	Laryngomalacia (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Failure to thrive (poor weight gain and/or poor longitudinal growth)	SNOMED-CT	R62.50	Unspecified lack of expected normal physiological development in childhood
Infantile Clinical Signs and Symptoms	Inclusion	Failure to thrive (poor weight gain and/or poor longitudinal growth)	SNOMED-CT	P92.6	Failure to thrive in newborn
Infantile Clinical Signs and Symptoms	Inclusion	Failure to thrive (poor weight gain and/or poor longitudinal growth)	SNOMED-CT	433476000	Failure to thrive in infant (disorder)
Infantile Clinical Signs and Symptoms	Inclusion	Poor feeding	SNOMED-CT	276717003	Poor feeding of newborn (finding)
Infantile Clinical Signs and Symptoms	Inclusion	Poor feeding	ICD-10	P92	Feeding problems of newborn
Infantile Clinical Signs and Symptoms	Inclusion	Osteochondral spurs	ICD-10	M25.7	Osteophyte
Infantile Clinical Signs and Symptoms	Inclusion	Osteochondral spurs	SNOMED-CT	235231000-119100	Osteophyte of bone (disorder)

Appendix B— Codes for perinatal HPP signs and symptoms

Category	Inclusion/ Exclusion Flag	Alexion Rule	Code Type	Code	Code Description
Perinatal					
Perinatal Clinical Signs and Symptoms	Inclusion	Polyhydramnios*	SNOMED-CT	268798004	Fetal or neonatal effect of maternal polyhydramnios (disorder)
Perinatal Clinical Signs and Symptoms	Inclusion	Polyhydramnios*	ICD-10	O40	Polyhydramnios
Perinatal Clinical Signs and Symptoms	Inclusion	Clubfoot	SNOMED-CT	630510001-19101	Fetal clubfoot (disorder)
Perinatal Clinical Signs and Symptoms	Inclusion	Hypoechogenic/ hypomineralized skull*	SNOMED-CT	93003001	Congenital anomaly of fetal head bones (disorder)
Perinatal Clinical Signs and Symptoms	Inclusion	Hypoechogenic/ hypomineralized skull*	SNOMED-CT	408771005	Ultrasound scan of fetal head abnormal (finding)
Perinatal Clinical Signs and Symptoms	Inclusion	Shortening**, bowing**, angulation of long bones**; fractures; beaded*, short**, or thin ribs**; metaphyseal radiolucencies**; osteochondral spurs (Bowdler spurs)**; severe chest deformity**; small or narrow thorax (chest size smaller than abdominal circumference)**; reduced mineralization of hands**; inconsistent ossification of vertebrae**; deficient or absent ossification of bones**	SNOMED-CT	199737005	Abnormal radiological finding on antenatal screening of mother (finding)
Perinatal Clinical Signs and Symptoms	Inclusion		ICD-10	O28.4	Abnormal radiological finding on antenatal screening of mother
Perinatal Clinical Signs and Symptoms	Inclusion		SNOMED-CT	169665005	Antenatal ultrasound scan abnormal (finding)
Perinatal Clinical Signs and Symptoms	Inclusion		ICD-10	O28.3	Abnormal ultrasonic finding on antenatal screening of mother
Perinatal Clinical Signs and Symptoms	Inclusion	Stillbirth	ICD-10	P95	Fetal death of unspecified cause
Perinatal Clinical Signs and Symptoms	Inclusion	Stillbirth	SNOMED-CT	237364002	Stillbirth (finding)
Perinatal Clinical Signs and Symptoms	Inclusion	Seizures	ICD-10	P90	Convulsions of newborn
Perinatal Clinical Signs and Symptoms	Inclusion	Seizures	SNOMED-CT	87476004	Convulsions in the newborn (disorder)
Perinatal Clinical Signs and Symptoms	Inclusion	Apnea	ICD-10	P28.4	Other apnea of newborn
Perinatal Clinical Signs and Symptoms	Inclusion	Apnea	SNOMED-CT	13094009	Apnea in the newborn (finding)

*Due to the nature of medical coding, fetuses *in utero* do not have their own medical record, and coding is through the mother's perspective and recorded in her chart.

**Specific codes for the asterisked fetal abnormalities above do not presently exist; high-level codes to indicate general abnormal findings are included.

Appendix B— Codes to rule out other causes of low ALP

Common to all age groups

Category	Inclusion/ Exclusion Flag	Alexion Rule	Code Type	Code	Code Description
Rule Out Low ALP	Exclusion	Familial hypophosphatemia	ICD-10	E83.31	Familial hypophosphatemia
Rule Out Low ALP	Exclusion	Cleidocranial dysplasia/ dysostosis	ICD-10	Q74.0	Other congenital malformations of upper limb(s), including shoulder girdle
Rule Out Low ALP	Exclusion	Cleidocranial dysplasia/ dysostosis	SNOMED-CT	65976001	Cleidocranial dysostosis (disorder)
Rule Out Low ALP	Exclusion	HPP (Rathbun disease)	ICD-10	E83.39	Other disorders of phosphorus metabolism
Rule Out Low ALP	Exclusion	HPP (Rathbun disease)	SNOMED-CT	190859005	Hypophosphatasia (disorder)
Rule Out Low ALP	Exclusion	Mseleni joint disease	ICD-10	Q77	Osteochondrodysplasia with defects of growth of tubular bones and spine
Rule Out Low ALP	Exclusion	Mseleni joint disease	SNOMED-CT	715470008	Brachydactylous dwarfism Mseleni type (disorder)
Rule Out Low ALP	Exclusion	Cancers and chemotherapy	SNOMED-CT	367336001	Chemotherapy (procedure)
Rule Out Low ALP	Exclusion	Cancers and chemotherapy	ICD-10	C00-D49	Neoplasms
Rule Out Low ALP	Exclusion	Cancers and chemotherapy	SNOMED-CT	55342001	Neoplastic disease (disorder)
Rule Out Low ALP	Exclusion	Cardiac bypass surgery	ICD-10	Z95	Presence of cardiac and vascular implants and grafts
Rule Out Low ALP	Exclusion	Cardiac bypass surgery	SNOMED-CT	232717009	Coronary artery bypass grafting (procedure)
Rule Out Low ALP	Exclusion	Surgery	SNOMED-CT	387713003	Surgical procedure (procedure)
Rule Out Low ALP	Exclusion	Surgery	CPT	10004-69990	Surgery
Rule Out Low ALP	Exclusion	Major trauma	ICD-10	T79	Certain early complications of trauma, not elsewhere classified
Rule Out Low ALP	Exclusion	Major trauma	SNOMED-CT	417746004	Traumatic injury (disorder)
Rule Out Low ALP	Exclusion	Multiple myeloma	ICD-10	C90.0	Multiple myeloma
Rule Out Low ALP	Exclusion	Multiple myeloma	SNOMED-CT	109989006	Multiple myeloma (disorder)
Rule Out Low ALP	Exclusion	Sepsis/multi-organ/hepatic failure	ICD-10	K72	Hepatic failure, not elsewhere classified
Rule Out Low ALP	Exclusion	Sepsis/multi-organ/hepatic failure	ICD-10	A41	Other sepsis
Rule Out Low ALP	Exclusion	Sepsis/multi-organ/hepatic failure	ICD-10	R65	Systemic inflammatory response syndrome (SIRS)
Rule Out Low ALP	Exclusion	Sepsis/multi-organ/hepatic failure	SNOMED-CT	91302008	Sepsis (disorder)
Rule Out Low ALP	Exclusion	Sepsis/multi-organ/hepatic failure	SNOMED-CT	59927004	Hepatic failure (disorder)
Rule Out Low ALP	Exclusion	Sepsis/multi-organ/hepatic failure	SNOMED-CT	57653000	Multiple organ failure (disorder)
Rule Out Low ALP	Exclusion	Starvation/acute caloric restriction	ICD-10	R63	Symptoms and signs concerning food and fluid intake
Rule Out Low ALP	Exclusion	Starvation/acute caloric restriction	ICD-10	T73.0	Effects of hunger (deprivation of food, starvation)

Category	Inclusion/ Exclusion Flag	Alexion Rule	Code Type	Code	Code Description
Rule Out Low ALP	Exclusion	Starvation/acute caloric restriction	ICD-10	E40-E46	Malnutrition
Rule Out Low ALP	Exclusion	Starvation/acute caloric restriction	ICD-10	F50.0	Anorexia nervosa
Rule Out Low ALP	Exclusion	Starvation/acute caloric restriction	ICD-10	F50.2	Bulimia nervosa
Rule Out Low ALP	Exclusion	Starvation/acute caloric restriction	ICD-10	F50.82	Avoidant/Restrictive food intake disorder
Rule Out Low ALP	Exclusion	Blood transfusion	SNOMED-CT	116859006	Transfusion of blood product (procedure)
Rule Out Low ALP	Exclusion	Adynamic renal osteodystrophy	ICD-10	N25.0	Renal osteodystrophy
Rule Out Low ALP	Exclusion	Adynamic renal osteodystrophy	SNOMED-CT	16726004	Renal osteodystrophy (disorder)
Rule Out Low ALP	Exclusion	Celiac disease	ICD-10	K90.0	Celiac (Coeliac) disease
Rule Out Low ALP	Exclusion	Celiac disease	SNOMED-CT	396331005	Celiac disease (disorder)
Rule Out Low ALP	Exclusion	Cushing's disease	ICD-10	E24	Cushing syndrome
Rule Out Low ALP	Exclusion	Cushing's disease	SNOMED-CT	190501008	Idiopathic Cushing's syndrome (disorder)
Rule Out Low ALP	Exclusion	Cushing's disease	SNOMED-CT	237737000	Pseudo-Cushing's syndrome (disorder)
Rule Out Low ALP	Exclusion	Hypomagnesemia	ICD-10	E83.42	Hypomagnesemia
Rule Out Low ALP	Exclusion	Hypomagnesemia	ICD-10	R79.0	Abnormal level of blood mineral
Rule Out Low ALP	Exclusion	Hypomagnesemia	ICD-10	E61.2	Magnesium deficiency
Rule Out Low ALP	Exclusion	Hypomagnesemia	SNOMED-CT	190855004	Hypomagnesemia (disorder)
Rule Out Low ALP	Exclusion	Hypozincemia	ICD-10	E60	Dietary zinc deficiency
Rule Out Low ALP	Exclusion	Hypozincemia	ICD-10	E83.2	Disorders of zinc metabolism
Rule Out Low ALP	Exclusion	Hypozincemia	ICD-10	R79.0	Abnormal level of blood mineral
Rule Out Low ALP	Exclusion	Hypozincemia	SNOMED-CT	238124008	Zinc deficiency (disorder)
Rule Out Low ALP	Exclusion	Milk-alkali syndrome	ICD-10	E83.52	Hypercalcemia/Milk-alkali disease or syndrome
Rule Out Low ALP	Exclusion	Milk-alkali syndrome	SNOMED-CT	43258006	Milk alkali syndrome (disorder)
Rule Out Low ALP	Exclusion	Nutritional deficiencies (vitamin C)	ICD-10	E64.2	Sequelae of vitamin C deficiency
Rule Out Low ALP	Exclusion	Nutritional deficiencies (vitamin C)	SNOMED-CT	386065001	Disorder of vitamin C (disorder)
Rule Out Low ALP	Exclusion	Osteogenesis imperfecta type II	ICD-10	Q78.0	Osteogenesis imperfecta
Rule Out Low ALP	Exclusion	Osteogenesis imperfecta type II	SNOMED-CT	78314001	Osteogenesis imperfecta (disorder)
Rule Out Low ALP	Exclusion	Pernicious anemia	ICD-10	D51.0	Vitamin B12 deficiency anemia (anaemia) due to intrinsic factor deficiency
Rule Out Low ALP	Exclusion	Pernicious anemia	SNOMED-CT	84027009	Pernicious anemia (disorder)
Rule Out Low ALP	Exclusion	Profound hypothyroidism	ICD-10	E03.9	Hypothyroidism, unspecified
Rule Out Low ALP	Exclusion	Profound hypothyroidism	ICD-10	E03.8	Other specified hypothyroidism
Rule Out Low ALP	Exclusion	Profound hypothyroidism	ICD-10	E00	Congenital iodine-deficiency syndrome
Rule Out Low ALP	Exclusion	Profound hypothyroidism	SNOMED-CT	83986005	Severe hypothyroidism (disorder)
Rule Out Low ALP	Exclusion	Radioactive heavy metal contamination	ICD-10	R78.79	Finding of abnormal level of heavy metals in blood
Rule Out Low ALP	Exclusion	Radioactive heavy metal contamination	SNOMED-CT	85866007	Toxic effect of heavy metal (disorder)
Rule Out Low ALP	Exclusion	Vitamin D intoxication	ICD-10	E67.3	Hypervitaminosis D
Rule Out Low ALP	Exclusion	Vitamin D intoxication	SNOMED-CT	27712000	Hypervitaminosis D (disorder)
Rule Out Low ALP	Exclusion	Wilson's disease	ICD-10	E83.01	Wilson's disease
Rule Out Low ALP	Exclusion	Bisphosphonate therapy	ICD-10	Z79.83	Long-term (current) use of bisphosphonates
Rule Out Low ALP	Exclusion	Bisphosphonate therapy	SNOMED-CT	723950005	Bisphosphonate therapy (procedure)

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