

# Electronic Medical Record and Clinical Evaluation of Two Patient Cohorts at Risk of Hypophosphatasia: Family History is an Underutilized Tool to Diagnose Patients with Rare Disease

**Christina Peroutka**

University of Virginia <https://orcid.org/0000-0001-9122-8550>

**Natalie M Beck**

Genome Medical, Inc.

**Ethan Gough**

Johns Hopkins University Bloomberg School of Public Health

**Mark Marzinke**

Johns Hopkins University School of Medicine

**Julie Hoover-Fong** (✉ [jhoover2@jhmi.edu](mailto:jhoover2@jhmi.edu))

Johns Hopkins University <https://orcid.org/0000-0002-1242-5626>

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## Research article

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# Abstract

**Background:** Family history (FH) is a powerful tool in screening and testing for chronic disease, oncologic conditions, and other genetic diagnoses, and is dependent upon observing patterns of features inherited across generations. Despite acceptance of FH as a fundamental part of a genetic medicine evaluation, there are limited data in other medical fields about its utility and benefit to patients.

**Methods:** We evaluated two patient populations at-risk of a rare metabolic condition— hypophosphatasia (HPP)—for the quality and quantity of FH data in their medical records. Population 1 was derived from patients seeking evaluation for a low bone density diagnosis at the Johns Hopkins Greenberg Center for Skeletal Dysplasias (GCSD); population 2 was identified through a targeted electronic medical record (EMR) query of low serum alkaline phosphatase (AP) measurements obtained through the Johns Hopkins Clinical Laboratory.

**Results:** In population 1 (n = 38), 27 (71%) were confirmed to have HPP. Of these, 14 (52%) presented with FH information in the EMR from 3 or more family members, and in 4 (15%) FH was suggestive of HPP. In population 2 (n=348), a similar proportion of subjects had 3 or more family members mentioned in the EMR (183 or 53%), but only 3 subjects (1%) included sufficient detail to determine that the family history was suggestive of HPP. Notably, once all patients in population 1 completed a medical genetics evaluation and HPP was confirmed, 20 (74%) had probable affected family members identified through obtaining and analyzing a pedigree. After cascade testing was offered to these family members, 17 patients (71%) from population 1 had at least one family member with HPP confirmed at a molecular level.

**Conclusions:** Based on these results, we propose that a full genetic medicine evaluation of those subjects from population 2 at highest risk of HPP would confirm HPP in many of them and identify similarly affected family members. We propose that taking a FH refines the diagnostic precision for patients with low bone density and identifies affected family members, and that HPP is likely more prevalent than previously thought.

## Background

Hypophosphatasia (HPP) is an ultra-rare inherited metabolic condition caused by variants in the tissue-nonspecific alkaline phosphatase gene (*TNSALP* or *ALPL*, OMIM 171760). There are six forms of disease, with variable age of presentation and severity: perinatal lethal, prenatal benign, infantile onset, childhood/juvenile onset, odontohypophosphatasia and adult-onset. Previous prevalence studies estimate severe HPP affects between 1 in 100,000 and 1 in 400,000 individuals, though population allele frequency suggest a prevalence closer to 1 in 6,370 for all forms(1). Inheritance may be autosomal recessive or dominant, with recessive forms often presenting earlier and with a more severe phenotype. HPP is characterized by pleiotropic manifestations ranging from perinatal lethal bone fragility, respiratory failure and seizures to isolated premature childhood tooth loss or adult-onset musculoskeletal pain,

fatigue and low bone density(1). Low serum alkaline phosphatase (AP) activity -based on age- and sex-specific norms is a key biochemical indicator of HPP(1), but is often unrecognized as pathologic. Enzyme replacement therapy (ERT) with asfotase alpha (Strensiq™) was approved by the FDA after demonstration of 97% survival in a cohort of treated patients with perinatal lethal HPP compared to 42% survival at 1 year of age in historical controls (2). Misdiagnosis of idiopathic osteoporosis and empiric treatment with bisphosphonates of patients with HPP is problematic since this treatment is contraindicated in HPP patients(3–5). Thus, although HPP is rare compared to idiopathic osteopenia/osteoporosis, individuals with HPP must be accurately diagnosed to receive effective disease-specific treatment and avoid empiric treatment with bisphosphonates, which is associated with significant adverse effects in this population.

Family history (FH) is an integral part of a patient's medical history and diagnostic process. Its importance has been recognized since the beginning of human history, with family histories recorded in the Old Testament and Hippocrates documenting their medical relevance. In current times, FH can be a powerful tool to optimize screening and testing for chronic disease,(6) cancer(7,8) and other conditions, (7,9–11) based on observed patterns of signs and symptoms across generations. FH tools in general medicine and oncology have been shown to have positive analytical validity (FH tools measure and obtain the information they are designed to obtain), clinical validity (FH demonstrates significant specificity and sensitivity for disease risk), and clinical utility (FH improves referral, screening and diagnosis rates), without significant negative social implications (12,13).

Despite its clinical value, other literature indicates FH recorded in the medical record is often incomplete, poorly documented and difficult to access(9,10,14,15). Other barriers to effective utilization of FH include limited understanding of the genetic basis of conditions, inability to obtain accurate and specific FH from patients, limited time and reimbursement to do so, inadequate tools for obtaining and interpreting the FH, and limited integration and functionality within the electronic medical record (7,9,10,14–16). FH is a fundamental part of the clinical genetic evaluation, and a three-generation pedigree is considered the standard of care.

Until now, there has been no published experience pertaining to the clinical utility of FH to diagnose individuals with HPP in the genetics clinic. In patients with HPP, a complete FH helps to differentiate HPP from other more common causes of low bone density and bone fragility. Given the spectrum of HPP disease manifestations, the broad variation within affected family members and unappreciated significance of low AP activity measurements, we hypothesize HPP is underdiagnosed. We suspect more patients with HPP can be identified simply by obtaining a FH, and suggest FH can refine prevalence data for rare disorders, such as HPP. We compared the individual and FHs of patients diagnosed with HPP in our genetics clinic to their own pre-clinical medical records and to the individual and FHs of subjects identified with low AP values in a separate electronic medical record (EMR) query. To our knowledge this is the first study to compare FHs before and after a clinical genetics evaluation in individuals seeking evaluation for a low bone mineral density disease and the FH of subjects at risk of this rare disease identified through an EMR query.

# Methods

## Study Population

The FH recorded in our institutional EMR was examined in two patient populations at risk of a low bone density condition, specifically HPP. The first population was identified from individuals evaluated at the Johns Hopkins Greenberg Center for Skeletal Dysplasias (GCSD) for a potential low bone density condition from April 2008 through March 2020. Each individual underwent a full clinical genetic evaluation, including collection of medical and family history, physical exam, and laboratory screening. Based on these results, individuals determined to have a high probability of HPP underwent molecular testing of the *ALPL* gene. Of those confirmed to have HPP, FH information recorded in the EMR preceding their initial clinical genetics encounter was also extracted for comparison to that obtained from the clinical genetics encounter.

The second population was identified through a query of all AP levels measured by the Johns Hopkins Hospital Core Laboratories on inpatients and outpatients from January 2013 through December 2015. In collaboration with the Johns Hopkins Center for Clinical Data Analysis (CCDA), the medical record numbers (MRNs) of subjects with one or more low AP levels (see Table 1) were then queried for discrete medical conditions associated with low bone density and low AP (not including HPP). This query included clinic site codes for oncologic treatment (as surrogate for malignancy), those with direct bilirubin  $\geq 5$  mg/dL (as surrogate for liver failure), and creatinine  $\geq 2.6$  mg/dL (as surrogate for renal failure), and ICD-codes associated with discrete diseases marked by low bone density and hypophosphatasemia (see Appendix A). Subjects identified through this query were excluded from further consideration. Of those remaining, subjects with 5 to 20 serum AP measurements performed over the study interval, of which  $\geq 80\%$  were low based on age- and gender-specific cutoffs (see Table 1), underwent a chart review for extraction of all available medical history potentially suggestive of HPP, as well as their FH. All data were abstracted under a waiver of consent. This process was approved by the Johns Hopkins Institutional Review Board.

## Data Collection

Presence or absence of the following FH documentation in the EMR was recorded for each subject in both populations: a three-generation pedigree, family history recorded within the text of medical note(s) and within the EMR FH table. Similarly, the depth of FH documentation was also recorded for the following: at least 1 family member, at least 3 family members and including more than one generation. For patients seen in the GCSD, confirmed FH of HPP was also recorded. Data were collected on uniform data collection forms, and definitions of data fields and a question-by-question (QXQ) document were compiled to ensure consistent data collection. These data were entered into a password-protected Research Electronic Data Capture (REDCap) database on an institutionally-supported server.

## Analysis

Analysis was performed using STATA (v13, StataCorp LP). (17) Summary statistics at the time of data collection of mean age and gender in both populations were tabulated. The proportion with each level and depth of FH documentation was calculated and compared between the 2 populations using chi-square analyses. The FH available for each subject was assessed for consistency with the HPP diagnosis. For the patients seen in the GCSD, the proportion with a FH suggestive of HPP after the clinical genetics evaluation was compared to the proportion who were confirmed to have the diagnosis.

## Results

The first population was identified from the clinical practice of the GCSD from April 2008-March 2020. As shown in figure 1, after clinical assessment, FH, and tailored biochemical assessment of patients presenting for evaluation of a potential low bone density (LBD) condition, 38 probands were considered to have a high likelihood of HPP. In 27 (71%), molecular testing of *ALPL* confirmed the diagnosis of HPP; notably, all AP measurements in these individuals were below the age- and sex-specific normal ranges (see Table 1). The FH that was recorded in the EMR prior to the genetic medicine evaluation showed that 63% had FH recorded in EMR notes for a minimum of one family member and 52% had FH recorded for at least three family members (Table 2). 52% also had FH recorded in the FH EMR table and none had a three generation pedigree (increasing to 100% after clinical evaluation in the GCSD clinic). 15% had FH suggestive of HPP prior to a clinical evaluation in the GCSD clinic, but this increased to 74% after the genetic clinical evaluation. After cascade testing of the family members suspected to also have HPP, 63% of population 1 had at least 1 family member (range 1-3) confirmed at a molecular level as having HPP. Thus from the 27 confirmed probands diagnosed with HPP in our clinic, 17 probands had 28 affected family members.

The second population at risk of hypophosphatasia (HPP) was identified as shown in Figure 2. There were 1,030,121 AP results generated by the Johns Hopkins Hospital (JHH) Core Laboratories from 163,016 inpatient and outpatient individuals over a 3-year period (January 2013 to December 2015). 7,129 individuals were eligible for chart review after exclusion of individuals who had other medical conditions associated with low AP activity measurements (Appendix A). The study population was narrowed further to 348 individuals, based on consistently low AP measurements per the algorithm in Figure 2. All available medical records from these individuals were reviewed for medical history features and FH suggestive of HPP. As shown in Table 2, 85% of this total population had FH recorded in EMR clinical notes for a minimum of one family member, while 53% had FH for three or more family members. 42% had FH recorded in the FH EMR table and 11% had a three generation pedigree recorded. 1% had FH information recorded in their EMR that was sufficient to suggest a diagnosis of HPP, although all 348 subjects reviewed had recurrent low AP measurements over the study interval.

As shown in Table 2, chi-square analysis showed that there are significantly more individuals in population 2 with a FH reported in at least one relative in the notes than in population 1 ( $p = 0.007989$ ). There is no difference in the proportion with a FH in at least one relative in the EMR table in population 1 as compared to population 2 ( $p = 0.316477$ ). Similarly, there is no difference in the proportion with a FH

for at least three relatives (including all possible sections - notes and/or the EMR table) in population 1 as compared to population 2 ( $p = 0.941319$ ). There are significantly more individuals in population 1 with a FH suggestive of HPP than in population 2 prior to clinical evaluation ( $p < 0.00001$ ).

## Discussion

Family history can identify individuals at risk of heritable rare diseases as well as identify affected family members who may also benefit from medical management. However, review of patients followed in our clinical center (population 1) and the results of our retrospective EMR study (population 2) indicate that FH is underutilized in clinical practice. This study began with the observation that most individuals diagnosed with HPP in our clinical center (population 1) had affected family members. These family members were identified for further testing only after collection of a 3 generation pedigree. This difference before and after collection of a comprehensive FH highlights its underutilization in medical practice.

Population 2, as outlined in Figure 2, involved an unbiased sampling of AP measurements in all patients evaluated over a 3 year period at our institution. After enriching the population for those at greatest risk of HPP and performing a comprehensive chart review of these remaining subjects, we found that the FH data available in the EMR were insufficient in most cases to assess the likelihood that their relatives had a low bone density condition that could be considered with the proband's history. The quantity of FH recorded in the EMR for population 2 showed comparable results to that of population 1. Less than half of individuals had FH recorded in the EMR FH table, the most readily available location in the EMR for healthcare providers to access and utilize these data. Most importantly, only 1% of this enriched population had sufficient detail in the recorded FH to allow for identification of a possible genetic skeletal condition in a relative. Even with chronically and clinically significantly low serum AP values, few providers ask disease-directed questions about family members.

In this study, FH was often mentioned in a clinical visit or note, but often included information about only 1 or 2 relatives and was difficult to access in the EMR or share among providers. We also found it was more common for FH to be recorded in notes versus in the FH table of the EMR, even though the FH table is more accessible during clinic appointments to other providers. At our institution, the structure of the FH table does not allow for visualization of FH across generations in the same way that a pedigree does. Some EMRs allow for pedigree creation from a FH table, but this function was not available at our institution when the study was performed. Additionally, pedigrees and other documents are catalogued within sections of the EMR which may be less accessible to providers at the point of care and unsearchable for recorded details of the FH. Specifically for the EMR study of population 2, a limitation of the EMR query was the inability to query by 'text search' in notes, FH table, or scanned documents. All data on the 348 charts were manually read and reviewed. It is possible that HPP was considered for additional individuals within the 7,129 patients with unexplained low serum AP, but who did not meet our refined criteria of 5 to 20 AP activity measurements performed over the study interval, of which  $\geq 80\%$  were low.

Another limitation of the current study is that lineage or side of the family was not a qualifier to include/exclude FH data. In the EMR population (population 2), we assumed all affected family members were from the same side of the family, thereby increasing risk of HPP. When assessed in-person, this may not actually be correct. In our description of these study cohorts (manuscript in preparation), 17% of population 2 were considered at-risk of HPP, but only 1% agreed to a clinical research evaluation. It is therefore not possible to know how many are actually affected with HPP and have affected family members. While the population seeking care at the GCSD (population 1) is a biased cohort of individuals who are referred due to concerns for bone disease, the data from this cohort underscore that in-person assessments including a three-generation pedigree adds substantially to the FH data available in the medical record, allows for identification of affected family members, and potentially refines disease prevalence data, especially for rare disease.

Research on FH to date suggests that publically accessible tools that generate a multigenerational FH prior to a clinic appointment help the provider to identify, screen and care for individuals with rare disease. (10,18) Our study highlights that 'rare' diseases may not be so rare if family history is collected and utilized in clinical practice. We designed a FH and risk-stratification tool for individuals with low bone mineral density that includes guidance for patients and providers based on other signs and symptoms, including serum AP levels (bonegenetics.org). After IRB approval, this research tool will refine the signs and symptoms that are the strongest predictors of HPP. Increased recognition of HPP is essential as the treatment of those patients varies from standard therapy for low bone density and bone fragility.

## Conclusions

Our study demonstrates that when a three-generation pedigree is obtained, more disease-specific evaluations can be pursued, more accurate diagnoses can be made, and affected family members are brought to medical attention through appropriate family risk counseling and screening. Although HPP is defined as an ultra-rare condition, the key features of bone fragility and decreased BMD overlap with osteopenia/osteoporosis, which is relatively common. In this study, when a three-generation FH and appropriate testing were completed, 27 patients were diagnosed with HPP in our center and 28 additional family members were also able to be diagnosed with HPP. This represents a doubling of disease prevalence of individuals diagnosed with this HPP, simply by taking a FH suggesting that HPP may not be ultra-rare. Despite the promising illustration of FH utilization within our clinical practice, challenges remain in applying EMR query of large data to identify individuals at-risk of inherited rare diseases, such as HPP, within a health system, especially when identification relies on FH documentation within the EMR.

## List Of Abbreviations

Alkaline phosphatase (AP)

Center for Clinical Data Analysis (CCDA)

Electronic medical record (EMR)

Enzyme replacement therapy (ERT)

Family history (FH)

Greenberg Center for Skeletal Dysplasias (GCSD)

Hypophosphatasia (HPP)

Low bone density (LBD)

Medical record numbers (MRNs)

Question-by-question (QXQ)

Research Electronic Data Capture (REDCap)

## Declarations

**Ethics approval and consent to participate:** This study was approved by the Johns Hopkins Institutional Review Board (IRB) Study 00066333 under a waiver of consent.

**Consent for publication:**– not applicable

**Availability of data and materials:** The datasets generated and/or analyzed during the current study are not publicly available due to being protected health information (PHI) but are presented in aggregate as was approved by the Johns Hopkins Data Trust Committee.

**Competing interests:** none

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**Authors' contributions:** CP and JHF completed the retrospective chart review. NB, CP and JHF completed the chart review of GCSD patients. MM completed the AP measurement query. EG assisted with the statistics.

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**Authors' information (optional):** see above.

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## Tables

**Table 1 - Lowest Normal Total Serum or Plasma Alkaline Phosphatase (AP) Activity (U/L)** Adapted from ARUP Laboratories and Colantonio et al 2012. (19,20)

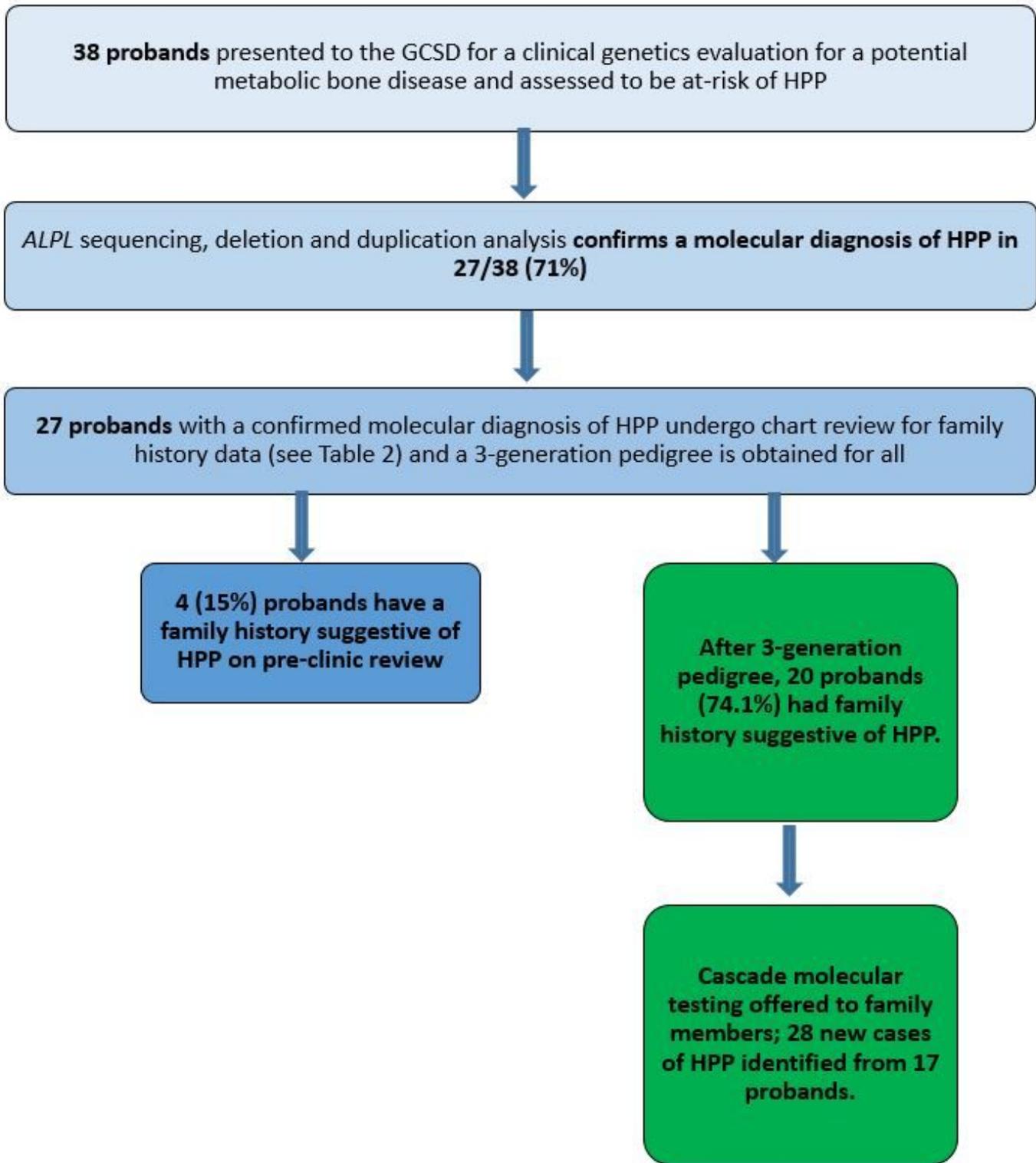
Age	Lowest Normal Total Serum or Plasma Alkaline Phosphatase Activity (U/L)	
	Male	Female
0-30 days	60	60
1-11 months	70	70
1-3 years	125	125
4-11 years	150	150
12-13 years	160	110
14-15 years	130	55
16-19 years	60	40
> 20 years	40	40

**Table 2 - Level and Depth of Family History Documentation** Population #1 includes patients seeking a clinical genetic evaluation at the GCSD. Population #2 includes subjects identified through EMR query. Family history documentation level (presence or absence) and depth (number of relatives documented) was recorded for each individual in both populations.

	Population #1 N=27	Population #2 N=348	Population #1 vs. #2 Chi-square test P value
	N (%)	N (%)	
Family history for $\geq 1$ relative in notes	17 (63)	295 (85)	8.5247 P = 0.007989
Family history for $\geq 1$ relative in EMR table	14 (52)	146 (42)	1.0034 P = 0.316477
Family history for $\geq 3$ relatives in notes or table	14 (52)	183 (53)	0.0054 P = 0.941319
3-generation pedigree	0 (0)	37 (11)	NA
Family history suggested HPP in clinical notes	4 (15)	3 (1)	50.6318 P <0.00001

$X^2$  (degrees of freedom, N = sample size) = chi-squared statistic value, p = p value.

## Figures



**Figure 1**

Algorithm used to evaluate patients presenting to the GCSD for potential metabolic bone disease then diagnosed with HPP from 4/2008-3/2020

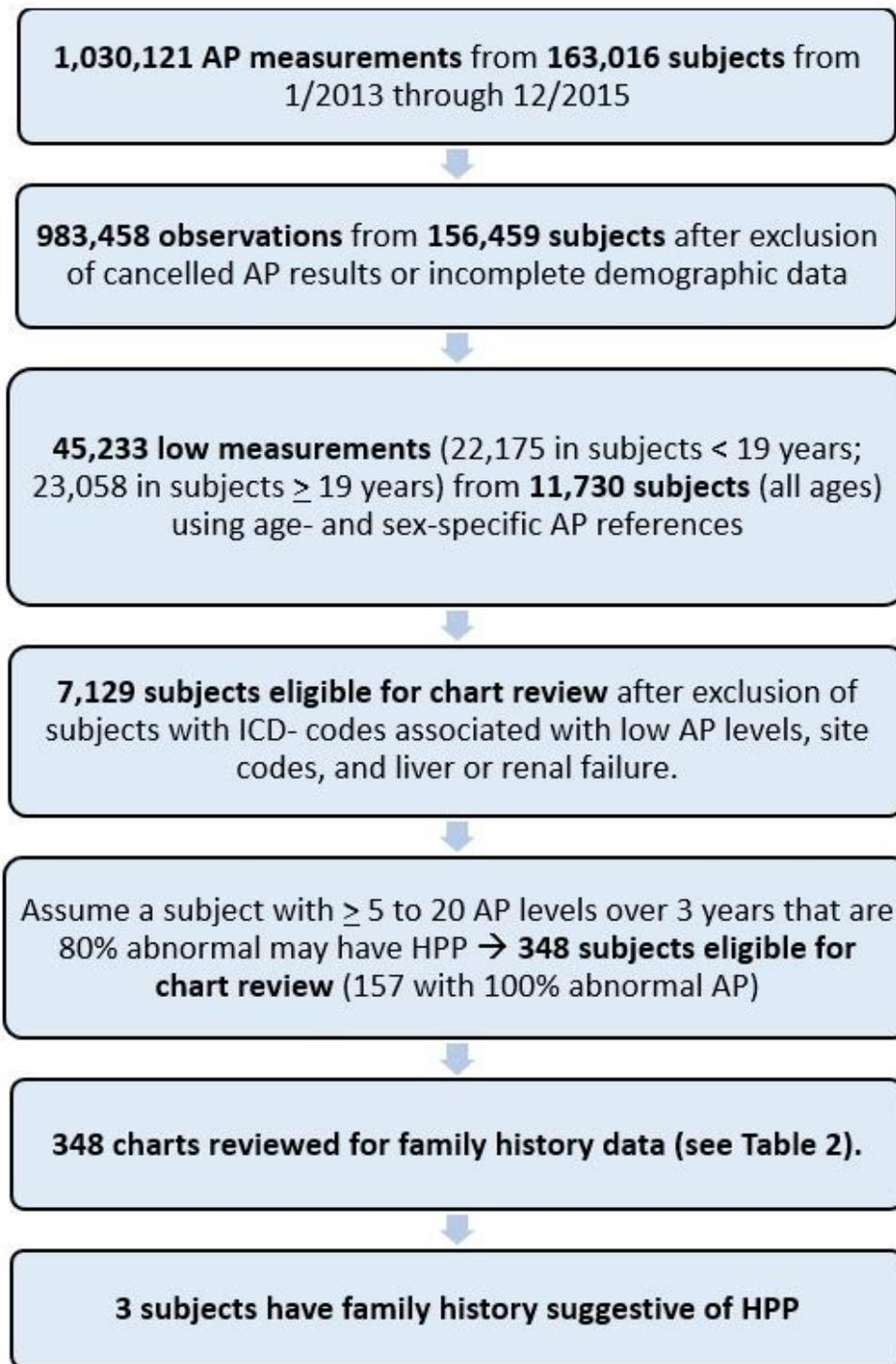


Figure 2

Algorithm used to identify individuals at risk of HPP through an EMR query

## Supplementary Files

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- [appendixA.docx](#)