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Phenotypic Analysis of Clinical Narratives Using Human Phenotype Ontology

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Abstract

Phenotypes are defined as observable characteristics and clinical traits of diseases and organisms. As connectors between medical experimental findings and clinical practices, phenotypes play vital roles in translational medicine. To facilitate the translation between genotype and phenotype, Human Phenotype Ontology (HPO) was developed as a semantically computable vocabulary to capture phenotypic abnormalities found in human diseases discovered through biomedical research. The use of HPO in annotating phenotypic information in clinical practice remains unexplored. In this study, we investigated the use of HPO to annotate phenotypic information in clinical domain by leveraging a corpus of 12.8 million clinical notes created from 2010 to 2015 for 729 thousand patients at Mayo Clinic Rochester campus and assessed the distribution information of HPO terms in the corpus. We also analyzed the distributional difference of HPO terms among demographic groups. We further demonstrated the potential application of the annotated corpus to support knowledge discovery in precision medicine through Wilson's Disease.

Keywords

Semantic Annotation; Human Phenotype Ontology; Phenotypic Analysis

Introduction

Phenotypes, defined as observable characteristics and clinical traits of diseases and organisms, have attracted increasing attention in the area of translational medicine by serving as the connectors between medical experimental findings and clinical practices. For example, in genomic medicine, phenotypes provide evidence to stratify and differentiate various groups of patients in order to discover specific hidden genotype-phenotype associations [1].

As a tool for annotating human phenotypic abnormalities, Human Phenotype Ontology (HPO) [2] has been developed as a controlled vacubulary for phenotypes by mining and integrating phenotype knowledge from medical literatures, Orphanet [3], Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources

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(DECIPHER) [4], and Online Mendelian Inheritance in Man (OMIM) [5]. HPO also provides associations with other biomedical resources such as Gene Ontology [6]. Multiple studies have utilized HPO for data annotation. For example, Taboada [7] developed a semantic annotation system to automatically extract rare disease information from PubMed literature using HPO. In addition, Westbury and his colleagues [8] used a HPO-based clustering approach to identify group of heritable bleeding and platelet disorders (BPD) cases. Zhu and her colleagues [9] leveraged HPO to develop a genetic testing knowledge base.

Here, we used HPO to annotate a large collection of clinical narratives consisting of all clinical notes generated from 2010 to 2015 at Mayo Clinic Rochester campus and assessed the distributional information of HPO terms. A case study was performed to demonstrate the potential application of the annotated data.

In the following, we describe the methods used for generating the annotated corpus. Next, we present and discuss our results. We then analyze the distributional differences among demographic groups and detail the case study followed by the conclusion and potential future directions.

Background and Materials

Clinical Data Collection

We collected all clinical notes created between 2010 and 2015 at Mayo Clinic Rochester campus with research authorization. The resulting corpus contains 12.8 million clinical notes corresponding to 729 thousand patients. Specifically, we limited our annotation to the diagnosis section of clinical notes for better extracting phenotype related terms.

The Unified Medical Language System and MetaMap

The Unified Medical Language System (UMLS) [10] is an integrated database that contains all key medical terminologies and their related resources. Each term in the UMLS has a Concept Unique Identifier (CUI) and belongs to a specific semantic type. MetaMap [11] is a configurable application that is able to map biomedical terms to UMLS Metathesaurus. In this study, we applied MetaMap with the UMLS version 2015 on free-text clinical notes to extract related terms as a preprocessing step.

Human Phenotype Ontology

We used the latest version of Human Phenotype Ontology (HPO) released on September 2016. The HPO contains four sub-ontologies as shown in Table 1, and each sub-ontology has its different focus on annotating area.

HPO package contains an ontology file that records all HPO phenotype terms with their synonyms and resource references (e.g., the UMLS). As shown in Figure 1, in the ontology hierarchical structure, *Menorrhagia (HP_0000132)* belongs to sub-ontology *Phenotypic Abnormality* and is listed as a subclass of *abnormal bleeding.* Two synonyms *abnormally heaving bleeding during menstruation* and *hypermenorrhea* are connected to it through object property *has_exact_synonym.* Moreover, *Menorrhagia* relates to a UMLS CUI

C0025323 through Web Ontology Language (OWL) axiom and object property *annotatedTarget.* The corresponding Resource Description Framework (RDF) representation in Figure 1 indicates such triple relationships. Although HPO has link to the UMLS, the current version of HPO has not been fully incorporated into the UMLS version after 2013. Due to this limitation, the combination of both HPO and the UMLS is able to make a more comprehensive annotation than using only one of them.

In addition, there is another clinical annotation file wrapped in HPO package that captures around 119,000 phenotype-disease associations where a majority of them (115,000) correspond to hereditary conditions. Take *Wilson's Disease* as an example, the HPO annotation file records 33 relevant phenotypes, e.g., *Proteinuria, Dementia*, and *Coma* etc.

Methods

Our annotation workflow is designed to leverage the UMLS and the corresponding NLP tool MetaMap. Figure 2 shows the overview of our annotation workflow, a combination of natural language processing (NLP) and semantic processing techniques. It includes two modules: i) the preprocessing module which leverages NLP techniques to extract key words from text; and ii) the semantic annotation module which maps the lexicon entries acquired from text to HPO terms and applies a greedy approach for each entry.

NLP Preprocessing Module

We first identify UMLS concepts in the diagnosis section of the clinical notes using MetaMap. We only keep UMLS concepts with the following phenotype-related semantic types: Disease or Syndrome (dsyn), Neoplastic Process (neop), Mental or Behavioral Dysfunction (mobd), Anatomical Abnormality (anab), Congenital Abnormality (cgab), Injury or Poisoning (inpo), Finding (fndg) and Sign or Symptom (sosy).

Semantic Annotation Module

Our annotation focuses on the main HPO sub-ontology *Phenotypic Abnormality* (HP_0000118) and its descendants. It contains 11,721 phenotype terms and 19,358 related synonyms defined in HPO or inferred from the linked UMLS CUIs. Our mapping includes two steps: we map UMLS concepts derived from the NLP preprocessing module to HPO terms using exact match, in case of ambiguity, we select the one with the smallest CUI number; and for HPO terms that failed to be mapped to the UMLS, the module then conducts another round of string matching refinement. Specifically, it reviews tokenized original text to check if there exists any possible candidate missed by MetaMap.

Results

The proposed annotation system was developed with Eclipse Standard/SDK version Luna 4.4.0. The interface to access MetaMap, the UMLS, and HPO were coded in Java programming language. In addition, we deployed the whole system on the Open Grid Scheduler (OGS) framework running on 64 bit Linux CentOS 6.8 servers hosted by Mayo Clinic to improve processing speed on large amounts of clinical notes.

In the following, to protect patients' privacy, any phenotypes with counts less than 11 were marked as <0.0015% or <11.

HPO Phenotype Coverage in Clinical Data

Overall, 3,241 out of 11,721 (27.7%) HPO phenotypes were extracted from 6,771,409 (52.8%) clinical notes. HPO has 23 abnormality categories. In our cohort, we counted the number of unique phenotypes and computed phenotype coverage for each category as shown in Figure 3. For example, *Abnormality of the nervous system* has the most phenotypes involved (599), e.g., *Anomia, Anxiety, Bone pain* and *Dysesthesia* while *Abnormality of the thoracic cavity* has no phenotype contained. Meanwhile, *Abnormality of the voice* holds a small group of phenotypes (11), including *Dysphonia, High pitched voice, Hoarse cry*, and *Laryngeal dystonia* etc. However, in terms of phenotype coverage, 78.6% (11 of 14) phenotypes under *Abnormality of the voice* were found. *Abnormality of the breast* also holds the second highest phenotype coverage as 55.6% (15 of 27). Since one phenotype can belong to more than one abnormality categories, in clinical notes, we found that 846 phenotypes are marked by 2 categories, 157 phenotypes dropped in 3 categories, 15 phenotypes are depicted by 4 categories, and only 1 phenotype is described by 5 categories.

Table 2 shows the top 10 frequent phenotypes as well as 10 phenotypes with relatively less frequent occurrences in clinical notes. We can see that many HPO common phenotype terms were found in cohort, such as *Hypertension, Hyperlipidemia, Apnea, or Anxiety*, etc.

We also noted our clinical notes contain phenotypes that related to rare diseases. For example, *Alacrima* is one of the features for *Triple A syndrome. Hemifacial hypertrophy* is a rare congenital disease. *Episodic tachypnea* often comes along with *Joubert syndrome. Alobar holoprosencephaly* is associated with *Holoprosencephaly. Barrel-shaped chest* is one of the symptoms of *Dyggve Melchior Clausen (DMC) syndrome*. *Chemodectoma* contributes to one of the signs caused by *Abdominal Chemodectomas with Cutaneous Angiolipomas*.

Demographic Phenotype Analysis

We retrieved patients' associated demographic information and assessed the phenotype distributional difference among demographic groups.

We analyzed the distribution of HPO abnormality categories among different age groups. Basically, we grouped age 0-17, 18-35, 36-54 and >55 as children and teenagers, young adults, mid adults, and old adults age groups. As shown in Figure 4, *Abnormality of the nervous system* is popular in each age group. *Abnormality of immune system* occurs more frequently in children and teenagers. *Abnormality of the digestive system* often comes with young adult patients. While *Abnormality of the cardiovascular, skeletal, metabolism/ homeostasis* and *respiratory systems* are common problems for mid adults but more common problems for old adults. In addition, *Immune system disorder*, *Abnormality of genitourinary system*, and *Neoplasm* have a high prevalence in old patients.

In total, there are 2,864 unique phenotypes found in male and 2,907 unique phenotypes detected in female. Based on patients' percentile for both genders, we found that

Hypertension, Apnea, Hyperlipidemia, Back pain, and *Obesity* are 5 most frequently occurred common phenotypes. We also conducted two case-control studies on male and female respectively to discover dominant phenotypes for each gender. We ranked phenotypes by descending order of odds ratios and filtered out phenotypes that are only associated with one specific gender (e.g., *Cryptorchidism* for male and *Amenorrhea* for female). With the odds ratio of 13.6, *Hypergonadotropic hypogonadism* is the phenotype that closely related to male (Table 3). Meanwhile, *Hirsutism* shows the highest odds ratio of 94.3 with female (Table 4). In general, top phenotypes in female held a relative higher average odds ratio.

We also extracted 29 races from clinical notes and picked 2 with the most population (excluding other and unknown races), which are White (519,098) and Black or Africa (8,835). Based on phenotype frequencies, we found top 5 common phenotypes for both races are *Hypertension, Apnea, Hyperlipidemia, Depression*, and *Back pain*, which highly overlapped with top 5 common phenotypes for male and female except *Depression.* We also conducted two case-control studies on White and Black or Africa patients to acquire significant phenotypes for each race. Table 5 shows top 5 significant White-specific phenotypes based on odds ratio. Based on literature review, we validated that *Basal cell carcinoma, Melanoma*, and *Macular degeneration* are highly related to patients in white race [12–14]. Table 6 shows top 5 significant Black or Africa-specific phenotypes based on odds ratio with the number of affected patients greater than or equal to 3. We found that 4 out of 5 top Black or Africa-specific phenotypes are related to genetic and rare diseases. *Scarring alopecia of scalp* is a rare disorder that destroys hair follicle. *Clitoral hypertrophy* is a congenital malformation and a rare condition. *Intellectual disability, profound* is related to *Lissencephaly*. *Spastic ataxia* is a symptom of *Autosomal Dominant Hereditary Ataxia.* Except those rare phenotypes, *Status asthmaticus* is a severe asthma. Literature indicated that *Scarring alopecia of scalp* and *Intellectual disability* are related to Black or Africa patients [15–16]. For other 3 phenotypes, even they occur in few patients but it may be worth to explore more as little evidence has been found about the relationship between them and Black or Africa patients in literature.

A Case Study of Phenotypic Analysis

Wilson's Disease (WD) is an autosomal recessive rare inherited disorder that makes copper accumulate in organs, and its diagnosis can be challenging as its signs and symptoms are often indistinguishable from those of other liver diseases, such as hepatitis. In this section, we conducted two case-control studies to demonstrate the potential of HPO-annotated data in supporting disease diagnosis. Among a total of 615,590 patients, we extracted 39 patients with confirmed diagnosis of WD and 63 patients suspected for WD but negative by genetic testing, leaving 615,488 patients with no clinical assertions or doubts for WD. Based on the three groups, two case-control studies were designed as follows: 1) To reveal significant phenotypes of WD, odds ratios of phenotypes were computed for 39 confirmed WD patients compared to 615,488 Non-WD patients; 2) To investigate the phenotypes significant for similar disease differentiation, odds ratios of phenotypes were computed for 39 confirmed WD patients compared to 63 patients suspected for WD.

Table 7 and 8 shows top 10 phenotypes ranked by odds ratio (with the number of affected patients greater than or equal to 3) representing significant clinical features of WD patients against the general population and the specific cohort with similar symptoms, respectively. Overall, odds ratio of phenotypes in the WD cohort against the general population were higher. Although the number of patients was relatively low, manual evaluation showed that all phenotypes are related to WD [17–19]. In contrast, odds ratio of phenotypes in the WD cohort against the similar cohort were relative lower, reflecting the reality that differential difficulties exist in the diagnosis of WD and WD similar diseases. However, according to [17], 7 phenotypes *Hypoalbuminemia, Nevus, Osteopenia, Cognitive impairment, Cirrhosis, Renal insufficiency*, and *Fever* are common symptoms of WD, of which only *Osteopenia* and *Cirrhosis* are covered by WD-related phenotypes recorded in HPO annotation file. The remaining are possible comorbidities highly occurring with WD. This analysis revealed the potential of these phenotypes in differentiating WD from similar diseases.

Discussion

Our study showed that almost half of the clinical notes contain no HPO terms. To investigate further, we extracted top 10 frequent phenotypes from those notes including *Fatigue*, *Pharyngitis, Dyslipidemia, Dermatoheliosis, Insomnia, Diabetes, Fibromyalgia, Snoring, Chronic Obstructive Airway Disease*, and *Rash*. In general, most of these phenotypes are not hereditary ones, and some of them are more generic than HPO terms (e.g., SNOMED CT terms [20]). For example, *Fatigue* covers HPO annotated phenotype *Exercise-induced muscle fatigue, Pharyngitis* gives a more general description of HPO annotated phenotype *Recurrent Pharyngitis*, and *Diabetes* is the super set of HPO annotated phenotype *Insulin-resistant diabetes mellitus*.

Note that in our case study, since *Wilson's Disease* is a rare disease, we were not able to provide a large sample size, which results in relative low odds ratio and high p-value when compared confirmed patients to the general population and suspected patients. In addition, in this research, to reduce the confounding factor of comorbidity, we picked phenotypes at the same year with WD diagnosis. In the future, to further address this issue, a more specific timestamp can be added to put restriction on diagnosed period. Currently, HPO records 33 phenotypes specifically related to WD. Although HPO coverage for WD is not sufficient, phenotypes in HPO can help on extracting all symptoms of diseases, making it possible to reveal significant phenotypes of WD by conducting case-control analysis. Therefore, it is possible to combine clinical notes with HPO to provide empirical evidences to further help diagnose and differentiate WD from similar diseases.

The integration of genotypic and phenotypic knowledge is an essential step to facilitate knowledge discovery in translational medicine. HPO, as a tool with linkage to gene databases and statistics of patients' percentile of phenotypes for each disease (e.g., 1% as very rare, 5% as rare), can be leveraged for this purpose. Especially for rare phenotypes, HPO makes it convenient for researchers to explore the potential genotype-phenotype associations.

Conclusions and Future Work

In this study, we used HPO to annotate phenotypes in clinical text for conducting phenotypic analysis. We demonstrated its potential in facilitating knowledge discovery.

In the future, we will try different ontologies and dictionaries to detect phenotypes from clinical notes and compare performances among them. Furthermore, a more specific diagnosis time range will be considered to largely reduce mischaracterization caused by complication and comorbidity. Moreover, we will use HPO with NLP and machine learning techniques to link various phenotypes with genes and drugs to perform knowledge discovery on gene disease and drug repositioning.

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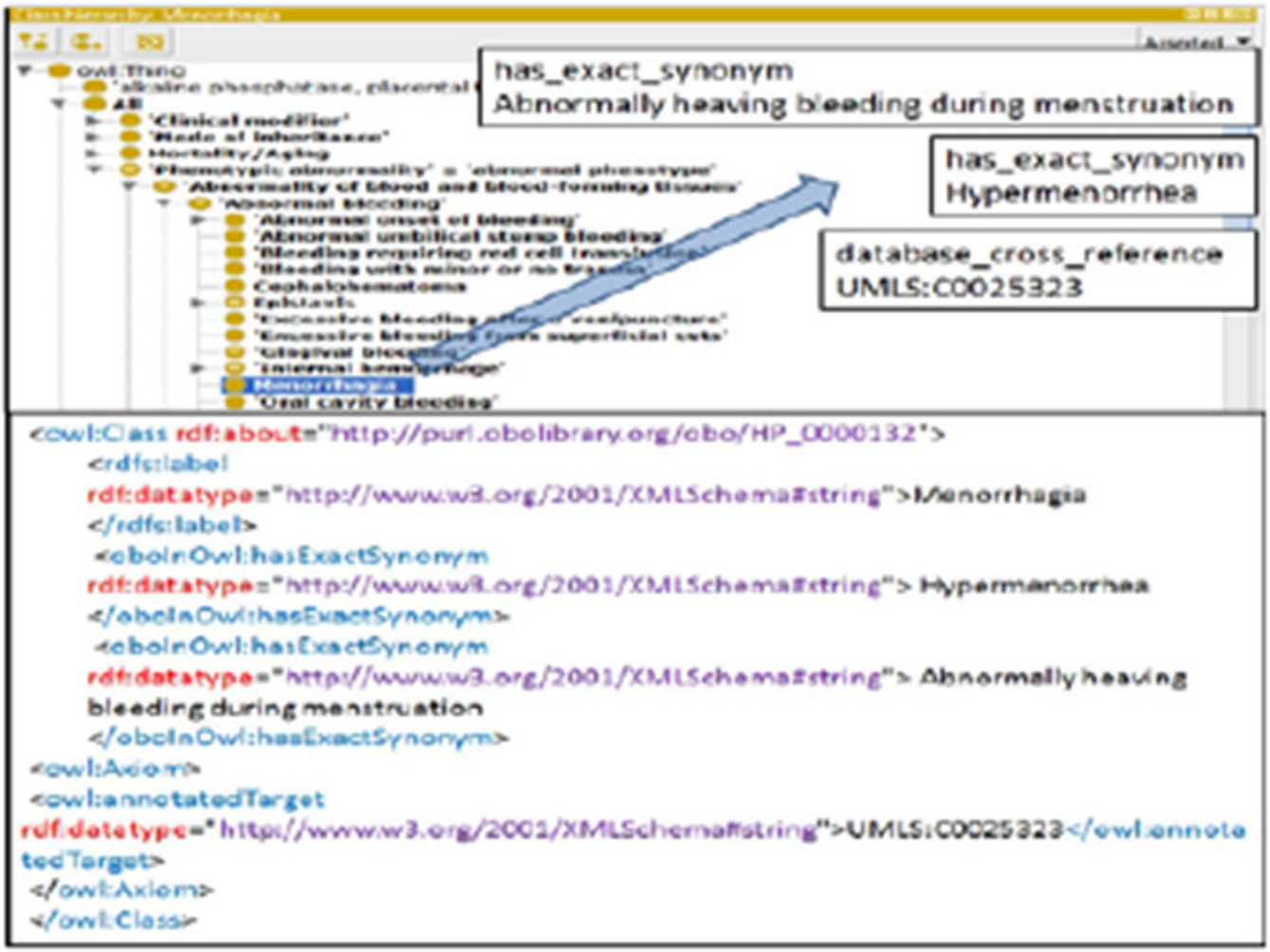

Figure 1–.
An Example of HPO Phenotype

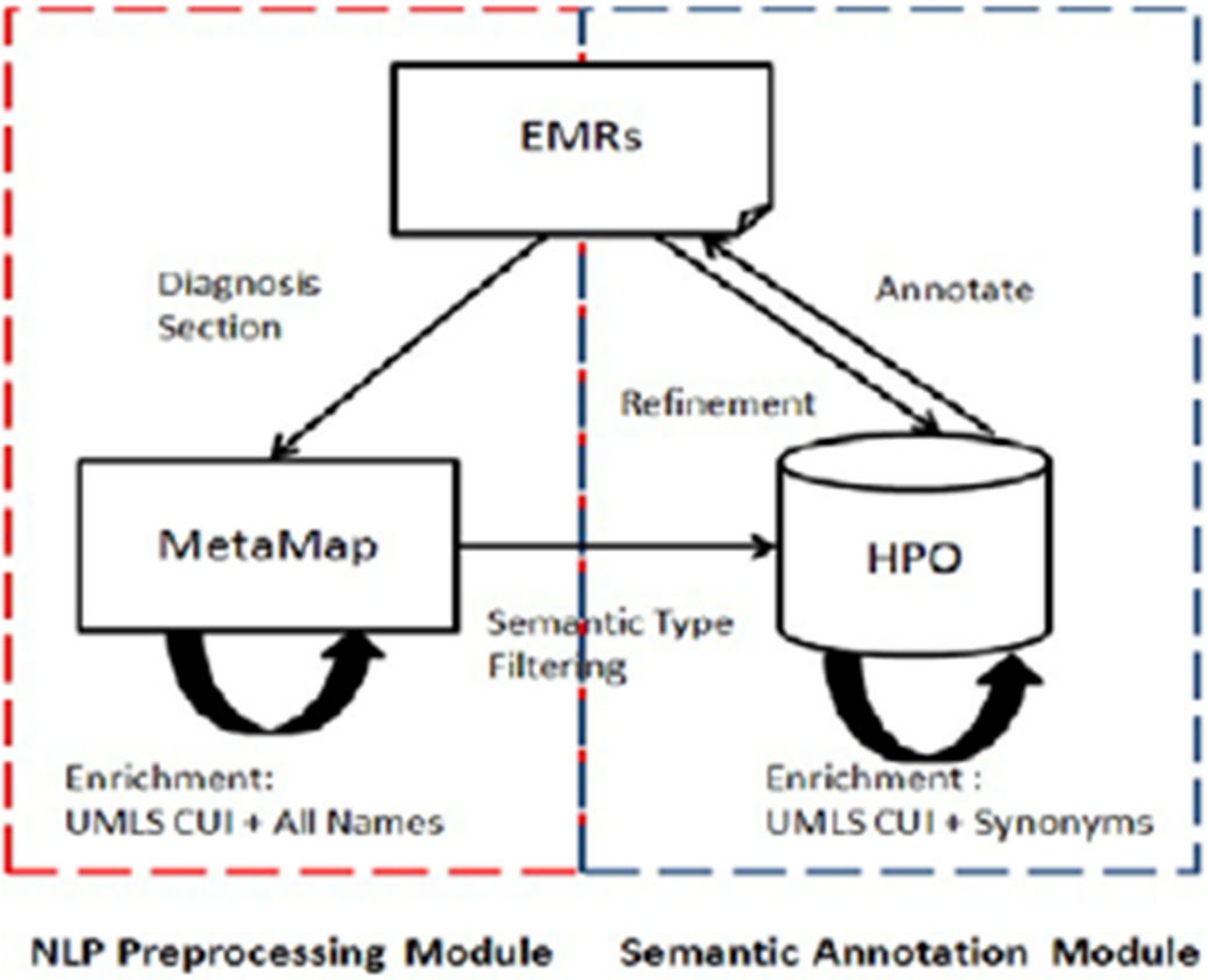

Figure 2–.
Annotation Work Flow

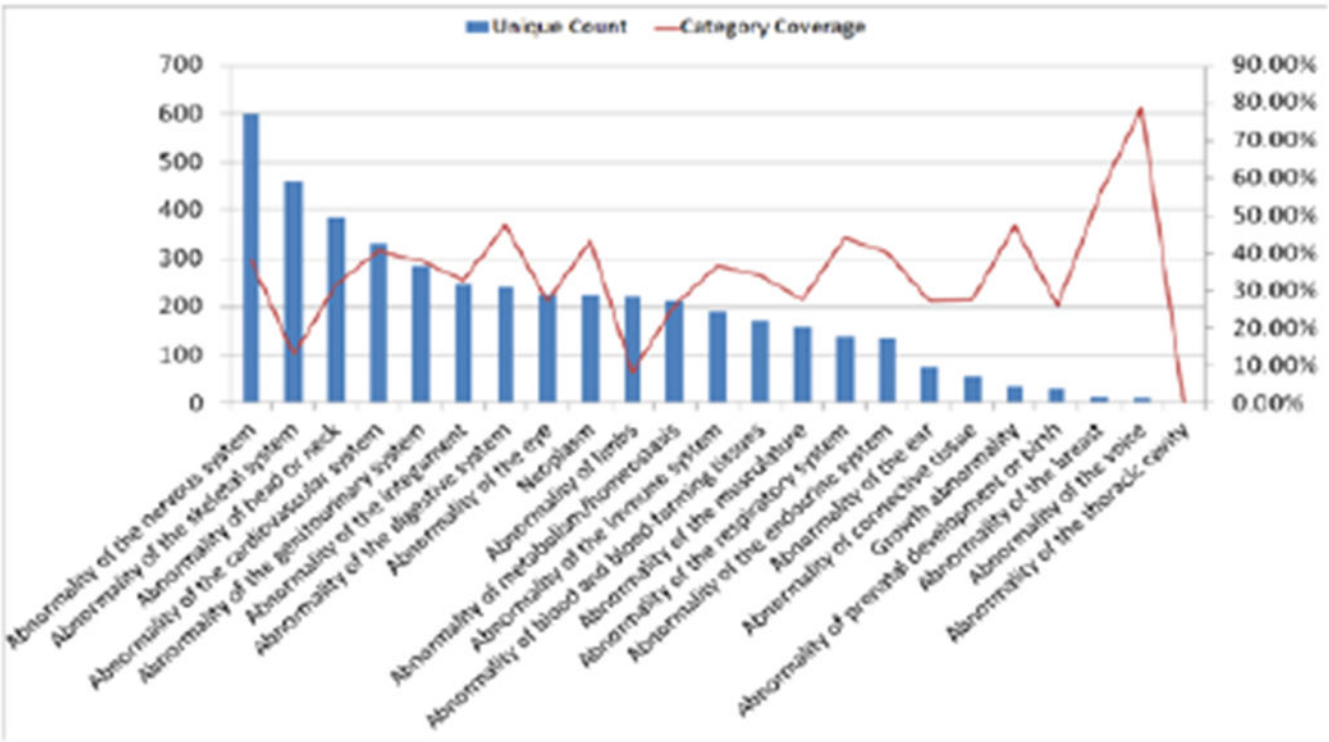

Figure 3–.
Distribution and Coverage for HPO Categories

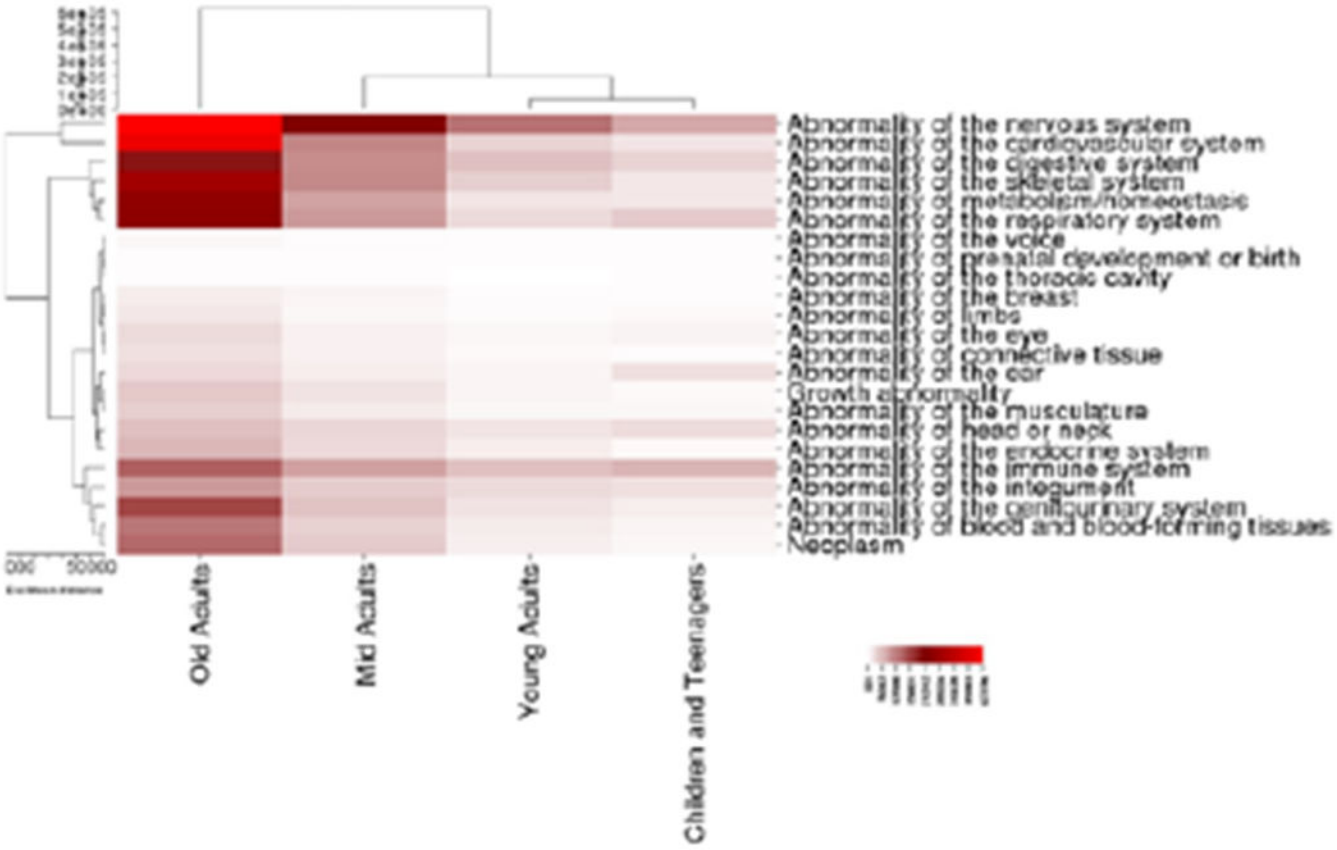

Figure 4–.
Distribution of Phenotypes across 4 Age Groups

Table 1–

HPO Sub-ontologies

Sub-ontology	Description
Phenotypic Abnormality	Main ontology of the HPO and covers most of the clinical abnormalities
Mode of Inheritance	Sub-ontology to describe mode of inheritance
Clinical Modifier	Sub-ontology with description of typical modifiers of clinical symptoms
Mortality/Aging	Sub-ontology that indicates time of death

Table 2–

Selected HPO Annotated Common/Rare Phenotypes

Common Phenotypes	Patients' Percentile	Rare Phenotypes	Patients' Percentile
Hypertension	19.8%	Alacrima	<0.0015%
Hyperlipidemia	15.2%	Intercostal retractions	<0.0015%
Depression	9.1%	Lattice retinal degeneration	<0.0015%
Apnea	8.6%	Hemifacial hypertrophy	<0.0015%
Back pain	8.5%	Decreased lacrimation	<0.0015%
Obesity	8.4%	Episodic tachypnea	<0.0015%
Sleep apnea	8.2%	Alobar holoprosencephaly	<0.0015%
Anxiety	8.2%	Barrel-shaped chest	<0.0015%
Headache	8%	Chemodectoma	<0.0015%
Arthritis	7.7%	Gastrointestinal carcinoma	<0.0015%

Table 3–

Top 5 Male-Specific Phenotypes

Phenotype	#Patients	odds ratio	p-value
Hypergonadotropic hypogonadism	136	13.6	2.0e-31
Violent behavior	20	11	3.9e-05
Dissecting aortic aneurysm	18	9.9	0.1e-03
Calf muscle hypertrophy	<11	9.9	0.9e-02
Sinusitis	9975	9.4	3.7e-158

Table 4–

Top 5 Female-Specific Phenotypes

Phenotype	#Patients	odds ratio	p-value
Hirsutism	1140	94.3	6.4e-298
Hepatocellular adenoma	114	26	4.9e-27
Bulimia	417	23.7	3.4e-94
Choroid plexus cyst	126	16.4	4.6e-27
Neural tube defect	55	12.5	1.8e-11

Table 5–

Top 5 White-Specific Phenotypes

Phenotype	#Patients	odds ratio	p-value
Basal cell carcinoma	12969	113.2	3.2e-92
Melanoma	20235	44.8	5.6e-136
Barrett esophagus	2899	16.5	1.9e-17
Telangiectasia	1884	16.1	1.6e-11
Macular degeneration	1330	11.3	8.5e-08

Table 6–

Top 5 Black or Africa-Specific Phenotypes

Phenotype	#Patients	odds ratio	p-value
Scarring alopecia of scalp	<11	25.2	0.5e-03
Clitoral hypertrophy	<11	14.7	0.3e-03
Intellectual disability, profound	<11	13.6	0.2e-02
Status asthmaticus	<11	11.8	0.1e-03
Spastic ataxia	<11	11.8	0.3e-02

Table 7–

Top 10 Phenotypes with Odds Ratio for Confirmed WD Patients to Non-WD related Patients

Phenotype	#Patients	odds ratio	p-value
Hepatic failure	<11	22.5	0.4e-03
Hypoalbuminemia	<11	12.1	0.2e-02
Cirrhosis	11	10.9	2.0e-08
Elevated hepatic transaminases	<11	7.29	0.9e-02
Splenomegaly	<11	7.27	0.9e-02
Ascites	<11	5.52	0.7e-02
Encephalopathy	<11	4.54	0.6e-02
Hepatitis	<11	4.02	0.5e-02
Lipoma	<11	3.51	0.6e-01
Thrombocytopenia	<11	3.18	0.9e-02

Table 8–

Top 10 Phenotypes with Odds Ratio for Confirmed WD Patients to Suspected Patients

Phenotype	#Patients	odds ratio	p-value
Hyperglycemia	<11	5.2	0.2
Hypoalbuminemia	<11	5.2	0.2
Nevus	<11	3.5	0.2
Esophagitis	<11	2.5	0.4
Osteopenia	<11	2.5	0.4
Cognitive impairment	<11	2.5	0.4
Hyperlipidemia	<11	2.54	0.2
Cirrhosis	11	2.08	0.2
Renal insufficiency	<11	2.06	0.3
Fever	<11	1.71	0.5