Finding missed cases of acute hepatic porphyria in a large Dutch general practitioner database using novel machine learning algorithm validated by expert clinicians.

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Introduction

- Acute hepatic porphyria (AHP) refers to a family of rare, genetic diseases characterized by potentially life-threatening attacks and for some patients chronic debilitating symptoms that negatively impact daily functioning and quality of life.[1,2,3]
- Despite frequent ER and/or GP visits and/or lengthy hospitalizations, patients are often misdiagnosed with time to diagnosis up to 15 years.
- We therefore developed a novel machine learning algorithm which learns through patients not confirmed for AHP, but who have clinical presentation similar to AHP.
- In this study, we partnered with a porphyria expert clinician to evaluate the effectiveness of our algorithm in finding potentially missed cases of AHP within a 2.5 million lives electronic health record (EHR) database.

Objectives

- To identify potential missed cases of AHP through the use of a novel machine learning algorithm.
- To shorten time to diagnosis for patients with AHP
- To create an algorithm and approach that is replicable to shorten time to diagnosis for AHP in other datasets.

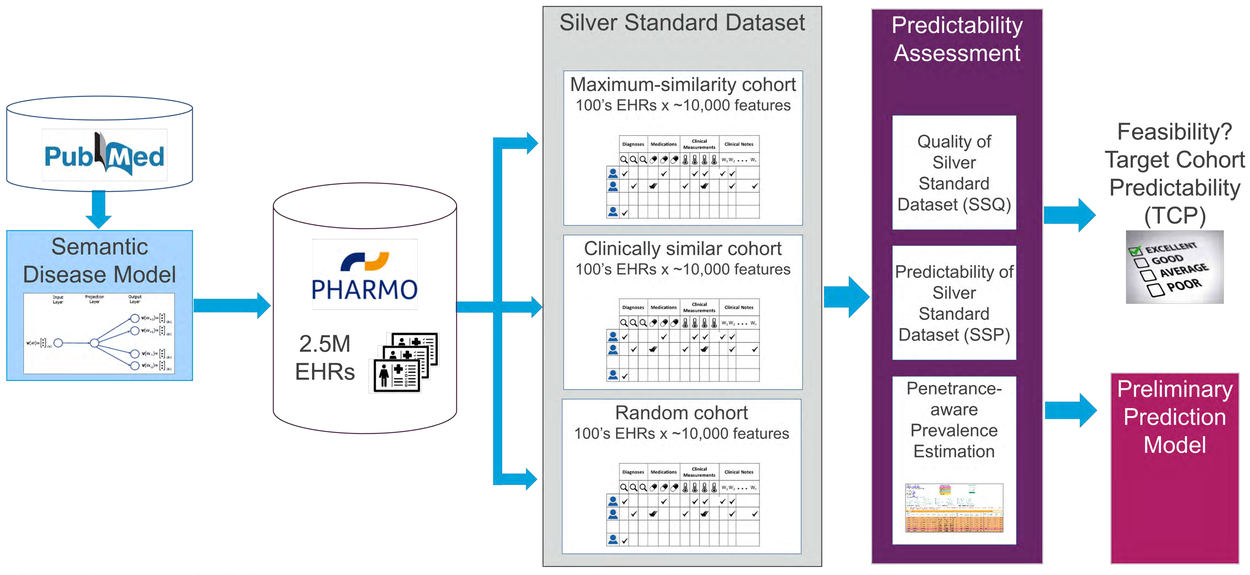
Methods

- All patient data was anonymized and provided to Pharmo Institute for Drug Outcomes Research by the data processor Stizon Foundation to ISO27001 and NEN7510 standards.

Methods continued

- The EHR database from Pharmo (GP-EHR-DB), contains de-identified records for 2.5M patients arising from their encounters with general practitioners (GPs) in The Netherlands[4].
- The information in GP-EHR-DB includes demographics data, ICPC diagnostic codes, ATC drug codes, and limited free-text clinical notes and lab results.
- In the 2.5m EHR dataset there were no records with clinical coding for AHP (the gold standard), so a candidate set was built, which we call a Silver Standard Labelled dataset (SSL-1).
- SSL-1 had to be refined into a second version 2 (SSL-2), see Figures 1 and 2 and was then assessed for suitability using a predictability assessment methodology.
- A preliminary prediction model (Figure 2) was built from the patients who have clinical presentation similar to AHP (maximum-similarity) using supervised machine learning. Then, to mitigate the adverse effects of unreliable labels, this model was optimally-refined using unsupervised learning from unlabeled EHRs.
- Importantly, we needed to abstract the full models to obtain simple models which can be deployed against GP EHR databases on-site using modest computational resources available.
- The cases identified by the algorithm with a high predicted probability of AHP and a small set of controls were provided to a clinical porphyria expert in a blinded manner.
- The specialist scored each candidate as ‘likely AHP’, ‘possible AHP’, ‘unlikely AHP’, ‘highly unlikely AHP’, ‘not AHP’, or ‘unable to assess’. The results of this review are reported in Table 1.

Figure 1: Developing a Preliminary Prediction Model



*Data transfer: November 21, 2017

Figure 2: Methodology Conceptual Overview to create a short list for a clinician

Volv process:

The Volv Approach addresses central challenge: lack of patients with confirmed gold standard diagnoses from which to learn predictive models.

1. Assemble a second draft silver standard labelled dataset, SSL-2, by refining SSL-1
2. Construct primary AHP patient prediction models, the *full models*, via noise-robust learning supervised by SSL-2
3. Abstract the full models to obtain *simple models* which can be deployed against GP EHR databases on-site using modest computational resources [5]

2.5M EHR Data Set

4. Use the simple models to detect candidate AHP patients, and store these (de-identified) patients’ EHRs in a secure dataset referred to as candidate patients AHP (CP-AHP)

Simple Prediction Model
331 EHRs (CP-AHP)

5. Compute the predicted probability that each of the patients in CP-AHP has AHP using the full models, and rank-order the patients according to these predicted probabilities

Full Prediction Model
42 EHRs

6. An AHP specialist practicing in The Netherlands was recruited and asked to review the EHRs for the top 42 candidate patients

Confirmed by Clinician:
33 EHRs

Step-wise methodology allows an evidence-based approach at each stage of the process

Results

Clinician Validation

- To support evaluation of the predictions, AHP specialists practicing in the Netherlands, including one of our co-authors, were asked to review the EHRs for the full list of top 42 candidate patients and 3 controls.
- The specialists scored each candidate as ‘likely AHP’, ‘possible AHP’, ‘unlikely AHP’, ‘highly unlikely AHP’, ‘not AHP’, or ‘unable to assess’. The results of this review are reported in Table 1.
- As can be seen, the list of the top 42 candidates includes 17 patients that the specialists assessed to be ‘likely AHP’ and 16 more deemed ‘possible AHP’, for a total of 42 plausible candidates (79% Precision@42).

Table 1: Results

	Total Number Undiagnosed Candidates (K)	Clinically Validated as Likely AHP	Clinically Validated as Possible AHP	Plausible Undiagnosed Candidates	Precision @K
Short List	20	14	4	18	90%
Full List	42	17	16	33	79%

- The short list of just the top 20 has even better precision, containing the 14 ‘likely AHP’ patients and 4 ‘possible AHP’ patients, for a total of 18 plausible candidates (90% Precision@20).
- None of the 3 controls were scored ‘likely AHP’ or ‘possible AHP’ by the Clinicians.
- Summarizing, the model created for AHP, learned using the patient finding algorithm without access to any patients with confirmed AHP diagnoses, is able to find high potential AHP candidates in a database of 2.5M EHRs.

Conclusions

- To our knowledge this is the first time a machine learning algorithm for AHP was built from patients who have clinical presentation similar to AHP.
- The clinical porphyria expert indicated 33/42 (79%) were plausible AHP patients.
- Our machine learning methodology is agnostic to the type of rare disease and has the potential to significantly shorten time to diagnosis in any rare disease.
- Indeed we would suggest that it is applicable and relevant to any difficult to diagnose disease.
- Next steps are:
  - Research collaborations with other expert porphyria clinicians interested in prospectively studying this algorithm in their hospital EHRs or other large national EMR datasets to find missed cases of AHP and shorten their time to diagnosis
  - Development of an interpretable version of this AHP model to be used in daily clinical practice

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