Evaluating Phenotype Algorithms using PheValuator
“A case definition describes characteristics that a patient must possess to have a disease from a clinical perspective.”

A collaborative approach to developing an electronic health record phenotyping algorithm for drug-induced liver injury.

An EHR phenotyping algorithm is the translation of the case definition into an executable algorithm that involves querying clinical data elements from the EHR.
What is a phenotype algorithm and why do we need them

• Tendency to equate the case definition with the phenotype algorithm (or the cohort definition) – the algorithm is the coded *approximation* of the case definition.
• Case definitions must be translated into algorithms for working with observational datasets
• There can be loss in translation in creating a phenotype algorithm from a case definition
• How much inaccuracy? → Need for validation
Validating a Phenotype Algorithm

<table>
<thead>
<tr>
<th>Phenotype Algorithm</th>
<th>Case Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included</td>
<td>True Positive (TP)</td>
</tr>
<tr>
<td>Not Included</td>
<td>False Negative (FN)</td>
</tr>
<tr>
<td>Case</td>
<td>False Positive (FP)</td>
</tr>
<tr>
<td>Non-Case</td>
<td>True Negative (TN)</td>
</tr>
</tbody>
</table>

Ex.: True Positive (TP) – when a subject included in the phenotype algorithm is a case

For a complete validation of the algorithm we need:

1) Sensitivity: TP / (TP + FN)
2) Specificity: TN / (TN + FP)
3) Positive Predictive Value (PPV): TP / (TP + FP)
4) Negative Predictive Value (NPV): TN / (TN + FN)
Validating Algorithms

- Many research studies have attempted to validate algorithms
- Traditional validation involves chart reviews of patients by clinical experts
  - Time consuming
  - Costly
  - At the end, generally only determine PPV
- Needed a replacement that could do this quicker, easier, and produce all the elements of validation (i.e., sensitivity, specificity, PPV)
PheValuator: Development and evaluation of a phenotype algorithm evaluator

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\textbf{ABSTRACT}

\textit{Background:} The primary approach for defining disease in observational healthcare databases is to construct phenotype algorithms (PAs), rule-based heuristics predicated on the presence, absence, and temporal logic of clinical observations. However, a complete evaluation of PAs, i.e., determining sensitivity, specificity, and positive predictive value (PPV), is rarely performed. In this study, we propose a tool (PheValuator) to efficiently estimate a complete PA evaluation.

\textit{Methods:} We used 4 administrative claims datasets: OptumInsight’s de-identified Clininformatics\textsuperscript{TM} Datamart (Eden Prairie, MN); IBM MarketScan Multi-State Medicaid; IBM MarketScan Medicare Supplemental Beneficiaries; and IBM MarketScan Commercial Claims and Encounters from 2000 to 2017. Using PheValuator involves (1) creating a diagnostic predictive model for the phenotype, (2) applying the model to a large set of randomly selected subjects, and (3) comparing each subject’s predicted probability for the phenotype to inclusion/exclusion in PAs. We used the predictions as a ‘probabilistic gold standard’ measure to classify positive/negative cases. We examined 4 phenotypes: myocardial infarction, cerebral infarction, chronic kidney disease, and atrial fibrillation. We examined several PAs for each phenotype including 1-time (1X) occurrence of the diagnosis code in the subject’s record and 1-time occurrence of the diagnosis in an inpatient setting with the diagnosis code as the primary reason for admission (1X-IP-1stPos).

\textit{Results:} Across phenotypes, 1X PA showed the highest sensitivity/lowest PPV among all PAs. 1X-IP-1stPos yielded the highest PPV/lowest sensitivity. Specificity was very high across algorithms. We found similar results between algorithms across datasets.

\textit{Conclusion:} PheValuator appears to show promise as a tool to estimate PA performance characteristics.
Overview of PheValuator Process

1. Large random sample
2. Train predictive model
3. Apply trained model
4. Evaluate
   - PPV, NPV
   - Sensitivity
   - Specificity
5. Probabilistic gold standard
Overview of PheValuator

1. Create a subject population of cases and non-cases for the model
2. Extract health data from the overall population – both cases and non-cases
3. Use regularized logistic regression (LASSO) to develop a model to discriminate between cases and non-cases
4. Use the model to determine the probability of subjects having the health outcome
5. Evaluate the phenotype algorithm
Example Results
Downloading PheValuator

https://github.com/OHDSI/PheValuator
Limitations of Phenotype Evaluation

• It’s only as good as the data
  – PheValuator estimates a probability of a health outcome similar to a clinician reviewing the data – if the data is sparse, there is less information to assess

• Some diseases are poorly differentiated from other diseases
  – E.g., Similar symptoms, treatment
  – Diagnostic testing is weak or non-existent
Where PheValuator has been Applied

In Public Domain
- PheValuator Journal Article
  - Myocardial Infarction
  - Ischemic Stroke
  - Atrial Fibrillation
  - Chronic Kidney Disease
- ICPE
  - Pulmonary Arterial Hypertension
  - Chronic Thromboembolic Pulmonary Hypertension
- OHDSI Symposium
  - Acute Renal Failure
  - Kidney Stone
  - Renal Cell carcinoma
  - Atopic Dermatitis
  - Psoriasis
  - Candidiasis
  - Melanoma

Internal Use
- Rheumatoid Arthritis
- Anemia
- Ankylosing Spondylitis
- Malignancies
- Crohn’s Disease
- Ulcerative Colitis
- GI Bleed
- Hemorrhagic Stroke
- Hyperlipidemia
- Hypothyroidism
- Depression
- Schizophrenia
- Serious Infection
- Blood Dyscrasias