Title : A case study evaluating the portability of an executable computable phenotype algorithm across multiple institutions and EHR environments

Corresponding author:

Jennifer A. Pacheco
645 N. Michigan Ave., Suite 630
Chicago, IL 60611
japacheco@northwestern.edu
312-503-6201

Authors:

Jennifer A. Pacheco[1*], Luke V. Rasmussen[1*], Richard C. Kiefer[2], Thomas R. Campion, Jr.[3], Peter Speltz[4], Robert J. Carroll[4], Sarah C. Stallings[5], Huan Mo[6], Monika Ahuja[3], Guoqian Jiang[2], Eric R. LaRose[7], Peggy L. Peissig[7], Ning Shang[8], Barbara Benoit[9], Vivian S. Gainer[9], Kenneth Borthwick[10], Kathryn L. Jackson[1], Ambrish Sharma[1], Andy Yizhou Wu[1], Abel N. Kho[1], Dan M. Roden[11,12], Jyotishman Pathak[3], Joshua C. Denny[4,11], William K. Thompson[1]

* Contributed equally to this work.

[1]Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
[2]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA
[3]Department of Healthcare Policy and Research, Weill Cornell Medicine, New York, NY, USA
[4]Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, USA
[5]Meharry-Vanderbilt Alliance, Vanderbilt University Medical Center, Nashville, TN, USA
[6]Department of Pathology, Loma Linda University Health, Loma Linda, CA, USA
[7]Department of Biomedical Informatics, Marshfield Clinic Research Institute, Marshfield, WI, USA
[8]Department of Biomedical Informatics, Columbia University, New York, NY, USA
[9]Research IS and Computing, Partners HealthCare, Harvard University, Somerville, MA, USA
[10]Henry Hood Center for Health Research, Geisinger, Danville, PA, USA
[11]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA
[12]Department of Pharmacology, Vanderbilt University Medical Center, Nashville, TN, USA

Keywords:

1. phenotype
2. electronic health records
3. algorithms
4. architecture
5. genomics
6. prostatic hyperplasia

Word count:

Abstract : 147 / 150
Manuscript: 1,992 / 2,000

ABSTRACT

Electronic health record (EHR) algorithms for defining patient cohorts are commonly shared as free-text descriptions that require human intervention to both interpret and implement. We developed the Phenotype Execution and Modeling Architecture (PhEMA, http://projectphema.org) to author and execute standardized computable phenotype algorithms. With PhEMA, we converted an algorithm for benign prostatic hyperplasia, developed for the electronic Medical Records and Genomics network (eMERGE), into a standards-based computable format. Eight sites (7 within eMERGE) received the computable algorithm and 6 successfully executed it against local data warehouses and/or i2b2 instances. Blinded random chart review of cases selected by the computable algorithm shows PPV ≥90%, and 3 out of 5 sites had >90% overlap of selected cases when comparing the computable algorithm to their original eMERGE implementation. This case study demonstrates potential use of PhEMA computable representations to automate phenotyping across different EHR systems, but also highlights some ongoing challenges.

INTRODUCTION

Electronic health records (EHRs) are designed primarily for clinical care and operations, which introduces limitations to the data when used for secondary purposes. These include data availability, accuracy, and information only available in unstructured narrative text.[1-3] To navigate these issues, researchers often develop "phenotype algorithms"– a set of criteria that specifies the analysis of data for identifying and studying patient populations with a given biomedical condition or indication.[4, 5]

When replication of results or additional statistical power is needed, a phenotype algorithm may be shared with other institutions for execution on their EHR data, using various methods and tools[6]. A common method used to share algorithms is as free-text descriptions of the algorithmic logic, possibly augmented with flowcharts and lists of codes from medical vocabularies. Implementing this description in a computable form (such as a database query) requires humans to interpret and make decisions for deployment, which can be error-prone and time-consuming.[7] An approach pursued via common data models (CDMs) is to organize EHR data according to a common standard. A CDM, such as those used by Observational Health Data Sciences and Informatics (OHDSI),[8] the National Patient-Centered Clinical Research Network (PCORnet),[9] and Informatics for Integrating Biology & the Bedside's (i2b2's)[10] Shared Health Research Informatics NEtwork (SHRINE),[11] can enable cross-site queries since the semantic and syntactic data organization are shared, but require transforming data to the CDM. Within the electronic Medical Records and Genomics (eMERGE) network,[12] the Phenotype KnowledgeBase (PheKB)[13] was created as an online environment to support collaboratively developing, validating, and sharing electronic phenotype algorithms across institutions, with a forum for clarifying implementation details as is often necessary. Truly portable phenotypes requiring little or no human interpretation and data transformation, would facilitate increasing the number of implementing institutions, but are not widely available.

To address this gap, we have developed the Phenotype Execution and Modeling Architecture (PhEMA; http://projectphema.org),[14] an open-source infrastructure for standards-based authoring, sharing and execution of phenotyping algorithms. PhEMA uses the National Quality Forum's (NQF's) Quality Data Model (QDM) and HL7's Health Quality Measure Format (HQMF)[15] to unambiguously model phenotype definitions, and enable the execution of these phenotype algorithms against different data representations, including local data warehouses (LDWs), and i2b2 data repositories. We describe a real-world use case for PhEMA: a computable algorithm for identifying patients with benign prostatic hyperplasia (BPH) from EHRs.

METHODS

BPH Phenotype Algorithm

BPH was chosen as a test phenotype for PhEMA in part because the case identification algorithm contains four of the most commonly used EHR data elements (demographics, diagnoses, procedures, and medications), all of the Boolean logical operators (*And*, *Or*, *Not*), a temporal relationship (age), and one aggregation function (count). Since the majority of sites in this study recently executed the algorithm for eMERGE, it also provided a baseline for comparisons against the results using PhEMA.

A single institution (Vanderbilt University) defined the original BPH phenotype algorithm for the eMERGE study (referred to as the "original algorithm"), which was modified by the authors for implementation within PhEMA (referred to as the "PhEMA algorithm"). The PhEMA algorithm used a combination of standard medical terminology codes for medications (RxNorm and NDC), diagnostic codes (ICD-9), and procedure codes (CPT). Although the original algorithm used natural language processing (NLP) on patients' problem lists, NLP was not included in the PhEMA algorithm due to a lack of standard representations of NLP.[16] The study population was defined as males age 40 and older who had no evidence in their EHR of prostate, penile, urethral, or bladder cancer. Within the PhEMA algorithm, the exclusion used just ICD-9 billing codes, although the original algorithm also used ICD-O-3

codes from tumor registries and mentions of these cancers in the problem list. The PhEMA algorithm selected cases only, who were defined as those in the study population with any BPH-related ICD-9 codes on 2 separate days, plus at least one BPH medication or BPH-related surgery code (Figure 1).

Translation of Algorithm into a Standardized, Executable Format

The modified PhEMA algorithm to detect BPH cases was represented using the PhEMA Authoring Tool (PhAT) (available at: https://github.com/PheMA/bph-use-case), by one of the authors (LVR). Since PhEMA relies on the presence of value sets (groups of medical terminology codes) to represent different medical concepts (e.g., medications, diagnoses), we first looked at the Value Set Authority Center (VSAC)[17] for existing value sets. Outside of the value set of "Male", no existing value sets met the need of our algorithm; therefore, the authors defined and published the necessary value sets within the VSAC for general use (also available at: https://github.com/PheMA/bph-use-case).

Given the use of QDM 4.1 [16, 18] within PhEMA, which accounts for the status of a data element (e.g., an active diagnosis, as opposed to the more abstract "diagnosis"), we included in our definition the relevant statuses for diagnoses, medications and procedures. This approach allows a more precise algorithm definition, as it removes the ambiguity of which statuses are appropriate.

The phenotype definition was exported from the PhAT into two executable KNIME workflows (KNIME AG, Zurich Switzerland, Figure 2): one workflow executed query definitions using i2b2 messaging (Figure 2A), and the other executed against an LDW (Figure 2B). KNIME was chosen as the execution engine as it is freely available, runs on multiple operating systems, and, most importantly, can connect directly to external systems that expose a web API. Furthermore, KNIME uses a modular graphical workflow interface that allows encapsulation of algorithm logic (the same across sites) from configuration details (variable between sites), allowing each site to configure the connection to their data without having to edit the algorithm's logic.[18, 19]

Upon review of the exported KNIME workflows, we identified opportunities to optimize their execution before distributing to sites. First, within sites' i2b2 instances, diagnosis status (active, resolved or inactive) was not explicitly described; thus, the 3 queries (one for each status) were collapsed into a single query. Second, by default the workflow returned multiple types of results within i2b2 for each query – a count, a list of patients, and a list of events. We edited the workflow to only return patient sets, to further reduce execution time. Finally, we removed the temporal relationship between BPH diagnoses and instead required patients have ≥2 BPH diagnoses, as some sites did not have visits associated with diagnoses in their i2b2 data.

Once given to the implementation site, each workflow required up to two local customization steps. First, the site must specify the connection details for their repository (i2b2 or LDW). Second, the site performed data customization if needed. For i2b2, this involved updating the ontology mapping so the correct concepts could be found; and for the LDW, editing template data queries to return the required data elements. Two members of the PhEMA team (JAP, LVR) guided this customization via remote screen sharing.

Execution of PhEMA BPH Algorithm

Eight sites (Columbia, Cornell, Geisinger, Harvard, Marshfield, Mayo, Northwestern, and Vanderbilt), executed the PhEMA BPH algorithm. Five eMERGE sites were able to assess if the same eMERGE subjects were identified by both their earlier custom implementation of the eMERGE BPH algorithm and the PhEMA implementation. To evaluate accuracy, we conducted manual blinded review of randomly selected cases using the chart abstraction form used for validating the eMERGE algorithm.

RESULTS

Execution

Of the eight sites, five executed the algorithm against their i2b2 repository, and four executed the algorithm against their LDW (Northwestern executed against both). Table 1 shows the number of cases identified using PhEMA, along with the number of males ≥40 years old in each site's data repository. Two sites (Harvard, Mayo) were unable to completely execute the KNIME workflow.

Site	Implementation				Validation					
					eMERGE Implementation				PhEMA Implementation	
	Data Repository	Patient Population	Males ≥40 y.o.	Males ≥40 y.o. w/ BPH	Cases Reviewed	Case PPV	Controls Reviewed	Control PPV	Cases Reviewed	Case PPV
Columbia	Local	eMERGE	1,441	56						
Cornell	i2b2	Entire LDW	1,064,560	7,805					98	96%
Geisinger	Local	eMERGE	5,453	1,039						
Harvard	i2b2	eMERGE	1,752	N/A						
Marshfield	i2b2	eMERGE	8,557	826	25	100%	25	100%	25	100%
Mayo	i2b2	Entire LDW	1,001,063	N/A						
Northwestern	i2b2 & Local	eMERGE	1,235	127	30	83%	10	80%	59	90%
Vanderbilt	Local	Entire LDW	1,201,845	5,118	50	100%	25	100%	50	92%
Total:			**2,284,843**	**14,974**	**105**		**60**		**232**	

Table 1. Results of PhEMA implementation and validation of eMERGE BPH case algorithm at each site. N/A indicates unable to complete the execution of the PhEMA KNIME workflow. Sites that were unable to complete a manual chart review as part of the validation are shaded in gray. PPV = Positive Predictive Value; LDW = Local Data Warehouse

Validation

Due to resource limitations, not all sites were able to perform a chart review. Results for those sites completing chart reviews are shown in Table 1. Three sites had validated the eMERGE implementation of the algorithm. The eMERGE case PPV was 100% at 2 of these 3 sites, and >80% at Northwestern (Table 1). Of the four sites that completed a chart review of the PhEMA implementation, all 4 sites reported PPV ≥90% with Northwestern increasing overall PPV for cases in their PhEMA implementation, and Vanderbilt decreasing.

Figure 3 shows the assessment of overlap in the cases between the eMERGE and PhEMA algorithm implementations for the 5 sites that successfully implemented both versions. Overall, we found that 3 sites had at least 90% overlap, and 2 sites had approximately half overlapping.

DISCUSSION

The ≥90% overlap at 3 of those 5 sites, and the fact that all of the PhEMA implementation case PPVs were ≥90%, a threshold often used in genetic studies,[4, 7] demonstrates the accuracy of PhEMA, and its ability to reproduce manual algorithm implementation results using a standardized computable format. We anticipated some differences due to the modifications of the algorithm, and PhEMA's current inability to handle NLP. Further discrepancies at Marshfield and Northwestern were traced to different interpretation and implementation of the eMERGE algorithm than originally intended (excluding all inclusion events at ages less than 40, omission of some ICD-9 and CPT codes, or requiring diagnoses to be made by the institution's providers). This did not greatly impact the validity of either eMERGE or PhEMA implementations, as PPV was sufficient in both instances (Table 2). However, the interpretation differences highlight the importance of the goal of PhEMA to produce computable portable phenotype algorithms, which eliminate the need for human interpretation of free-text.

Although current algorithm methodology can and does result in PPVs that demonstrate sufficient accuracy to power GWAS,[20-27] PhEMA seeks to improve the efficiency and portability of executing across different sites by producing computable algorithms; however, manual site-specific configuration was needed. Informal observation suggests that executing a PhEMA phenotype takes less time to implement than a corresponding free-text description, although additional time is required by the algorithm author to create a computable definition using PhAT. For example, Geisinger configured and executed the PhEMA implementation in less than a day, which was considerably less time than it took to create their custom implementation for eMERGE. Our approach can be compared to networks with a CDM where similar successes have been reported for portable, computable phenotype algorithms, but with the requirement that all sites have a pre-coordinated data model.[28, 29]

Most of the difficulties we had in executing across sites were technical. Table 2 details five of the largest issues that we worked through with sites. We purposefully limited the amount of time to troubleshoot issues as a proxy measure for portability, and thus marked Harvard's and Mayo's executions as unable to complete. Mayo's issue provided insight that the de-compositional approach used to construct our workflows extracted patients separately for each data element (e.g., all males, all individuals >=40 years old, etc.), then joined them all together, rather than use a stepwise approach to find patients with the first data element (males), and then of those, patients with the second data element (males >=40 years old). Additional notes regarding our analyses of these issues are available in Table 2.

Table 2. Technical issues encountered with implementation of the BPH phenotype at other sites.

Issue	**Analysis**	**Resolution**
Terms in BPH value sets were not represented in the site's local ontology.	A cursory review by the site implementer would allow them to	Manually edit the terms used in a value set to include the local terms for the institution. (e.g.,

	determine which terminology(ies) they did not have loaded.	manually identify all NDC codes related to the RxNorm codes for medications, then add those NDC codes to the list of terms in the medication value set)
The Harvard development server was able to execute the workflow, but the production instance returned an HTTP 503 “Service Unavailable” error.	After engaging the site’s server team, no additional information was available to explain this error. Even when the server was returning a 503 response to the KNIME workflow, the i2b2 web client that uses the same services was available and responsive. This indicated that the actual service was available, but may be responding in this way to the frequency of the requests from KNIME.	This has not yet been resolved.
KNIME workflow would not complete execution against the Mayo i2b2 instance.	The i2b2 instance was the largest of the sites involved with this study, at over 9 million patients. We confirmed that this was not a limitation of the i2b2 platform, by manually creating and executing the BPH algorithm using their i2b2 web interface. Instead, we identified	This has not yet been resolved.

	scalability issues with our KNIME workflow construction process that lead to computational bottlenecks, especially when processing queries against a repository of this size.	
Execution speed of the workflow is slow.	Given the decompositional nature of the query, where individual criteria are each queried and then later combined, we confirmed that the overall execution time would be increased compared to executing a single, final query.	Future work includes improving our execution platform to increase overall speed.
Unable to connect to the local data warehouse.	Sites frequently received connection errors. When working with sites to resolve these, we identified that they were legitimate errors, but that the way they were reported back to users was not helpful and did not offer any resolution.	Future work includes improving the feedback from the execution platform to describe (if possible) what may be causing a connection issue.

Finally, because selecting a random subset from the entire population for manual review was not feasible, our methodology for selection of charts for manual review was biased. We selected only from cases found by the execution of our phenotype algorithms, plus at some sites from a convenience sample (eMERGE subjects).

Future work

Given the lessons learned here, the PhEMA project is restructuring our approach to executing phenotype algorithms. We are developing an execution architecture that will better leverage efficiencies that can be gained by providing the entire (or large portions of the) phenotype query to the underlying database system. In addition, we are expanding our support for the other common data models, such as OMOP/OHDSI, for further cross-platform compatibility.

CONCLUSION

This case study demonstrates that a phenotype authoring system, such as PhEMA, could result in efficient and accurate implementations of EHR phenotype algorithms across multiple sites, and support differences in underlying data repositories. In this study, we identified some limitations in the current execution approach, which will provide guidance in future development.

Acknowledgements

The authors wish to thank Bilal Chughtai, Yiye Zhang, and Todd Edwards for assisting with chart reviews, verifying final numbers at their respective institutions, as well as helpful advice during the completion of the project.

Competing Interests

None.

Funding

PhEMA is funded by NIH through grant R01GM105688.

This phase of the eMERGE Network was initiated and funded by the NHGRI through the following grants: U01HG8657 (Group Health Cooperative/University of Washington); U01HG8672 (Vanderbilt University Medical Center); U01HG6379 (Mayo Clinic); U01HG8679 (Geisinger Clinic); U01HG8680 (Columbia University Health Sciences); U01HG8673 (Northwestern University); and U01HG8676 (Partners Healthcare/Broad Institute).

Portions of this research were supported by the W.R. Wiley Environmental Molecular Science Laboratory, a national scientific user facility sponsored by the U.S. Department of Energy's Office of Biological and Environmental Research and located at PNNL. PNNL is operated by Battelle Memorial Institute for the U.S. Department of Energy under contract DE-AC05-76RL0 1830.

Contributors

JAP and LVR contributed equally to this work, and developed the initial drafts of the manuscript. LVR, RCK, PS, HM, TRC, JAP, JP, JD, WKT and GJ designed and/or developed the software architecture. JAP, LVR, RCK, TRC, RJC, SCS, HM, MA, ERL, PLP, NS, BB, VSG, KB, and KLJ facilitated execution of the BPH phenotype algorithm versions at their respective institutions. AS, AYW, ANK, HM, SC, RJC, JD, MA, TRC, JP, ERL and PLP conducted chart reviews at their respective institutions.

JAP, KLJ, BB, MA, TRC, RCK, ERL, PLP, KMB, SC, RJC, JD, and NS analyzed the results at their respective institutions. JP, JD, WKT and GJ led the conception, and provided oversight and interpretation, of the project and the manuscript. SCS, RJC, JD and DMR developed the eMERGE BPH phenotype algorithm used for this study. All authors reviewed and approved of the submitted manuscript, and have agreed to be accountable for its contents.

References

1. Denny JC. Chapter 13: Mining electronic health records in the genomics era. *PLoS Comput Biol*. 2012;8(12):e1002823.
2. Wei W-Q, Denny JC. Extracting research-quality phenotypes from electronic health records to support precision medicine. *Genome Medicine*. 2015;7(1):41.
3. Rasmussen LV, Thompson WK, Pacheco JA, et al. Design patterns for the development of electronic health record-driven phenotype extraction algorithms. *J Biomed Inform*. 2014;51:280-6.
4. Shivade C, Raghavan P, Fosler-Lussier E, et al. A review of approaches to identifying patient phenotype cohorts using electronic health records. *J Am Med Inform Assoc*. 2014;21(2):221-30.
5. Mo H, Thompson WK, Rasmussen LV, et al. Desiderata for computable representations of electronic health records-driven phenotype algorithms. *J Am Med Inform Assoc*. 2015;22(6):1220-30.
6. Xu J, Rasmussen LV, Shaw PL, et al. Review and evaluation of electronic health records-driven phenotype algorithm authoring tools for clinical and translational research. *J Am Med Inform Assoc*. 2015;22(6):1251-60.
7. Newton KM, Peissig PL, Kho AN, et al. Validation of electronic medical record-based phenotyping algorithms: results and lessons learned from the eMERGE network. *J Am Med Inform Assoc*. 2013;20(e1):e147-54.
8. Hripcsak G, Duke JD, Shah NH, et al. Observational Health Data Sciences and Informatics (OHDSI): Opportunities for Observational Researchers. *Stud Health Technol Inform*. 2015;216:574-8.

9. Collins FS, Hudson KL, Briggs JP, et al. PCORnet: turning a dream into reality. *J Am Med Inform Assoc*. 2014;21(4):576-7.
10. Murphy SN, Weber G, Mendis M, et al. Serving the enterprise and beyond with informatics for integrating biology and the bedside (i2b2). *J Am Med Inform Assoc*. 2010;17(2):124-30.
11. Weber GM, Murphy SN, McMurry AJ, et al. The Shared Health Research Information Network (SHRINE): a prototype federated query tool for clinical data repositories. *J Am Med Inform Assoc*. 2009;16(5):624-30.
12. Gottesman O, Kuivaniemi H, Tromp G, et al. The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future. *Genet Med*. 2013;15(10):761-71.
13. Kirby JC, Speltz P, Rasmussen LV, et al. PheKB: a catalog and workflow for creating electronic phenotype algorithms for transportability. *J Am Med Inform Assoc*. 2016;23(6):1046-52.
14. Rasmussen LV, Kiefer RC, Mo H, et al. A Modular Architecture for Electronic Health Record-Driven Phenotyping. *AMIA Jt Summits Transl Sci Proc*. 2015;2015:147-51.
15. Health Level 7 (HL7). HL7 Version 3 Standard: Representation of the Health Quality Measure Format (eMeasure) Release 1 2018 [April 20, 2018]. Available from: http://www.hl7.org/implement/standards/product_brief.cfm?product_id=97.
16. Thompson WK, Rasmussen LV, Pacheco JA, et al. An evaluation of the NQF Quality Data Model for representing Electronic Health Record driven phenotyping algorithms. *AMIA Annu Symp Proc*. 2012;2012:911-20.
17. Bodenreider O, Nguyen D, Chiang P, et al. The NLM value set authority center. *Stud Health Technol Inform*. 2013;192:1224.
18. Mo H, Jiang G, Pacheco JA, et al. A Decompositional Approach to Executing Quality Data Model Algorithms on the i2b2 Platform. *AMIA Jt Summits Transl Sci Proc*. 2016;2016:167-75.
19. Mo H, Pacheco JA, Rasmussen LV, et al. A Prototype for Executable and Portable Electronic Clinical Quality Measures Using the KNIME Analytics Platform. *AMIA Jt Summits Transl Sci Proc*. 2015;2015:127-31.

20. Dumitrescu L, Ritchie MD, Denny JC, et al. Genome-wide study of resistant hypertension identified from electronic health records. *PLoS One*. 2017;12(2):e0171745.
21. Jackson KL, Mbagwu M, Pacheco JA, et al. Performance of an electronic health record-based phenotype algorithm to identify community associated methicillin-resistant Staphylococcus aureus cases and controls for genetic association studies. *BMC Infect Dis*. 2016;16(1):684.
22. Mosley JD, Shaffer CM, Van Driest SL, et al. A genome-wide association study identifies variants in KCNIP4 associated with ACE inhibitor-induced cough. *Pharmacogenomics J*. 2016;16(3):231-7.
23. Hall MA, Verma SS, Wallace J, et al. Biology-Driven Gene-Gene Interaction Analysis of Age-Related Cataract in the eMERGE Network. *Genet Epidemiol*. 2015;39(5):376-84.
24. Malinowski JR, Denny JC, Bielinski SJ, et al. Genetic variants associated with serum thyroid stimulating hormone (TSH) levels in European Americans and African Americans from the eMERGE Network. *PLoS One*. 2014;9(12):e111301.
25. Ritchie MD, Verma SS, Hall MA, et al. Electronic medical records and genomics (eMERGE) network exploration in cataract: several new potential susceptibility loci. *Mol Vis*. 2014;20:1281-95.
26. Arking DE, Pulit SL, Crotti L, et al. Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization. *Nat Genet*. 2014;46(8):826-36.
27. Almoguera B, Vazquez L, Mentch F, et al. Identification of Four Novel Loci in Asthma in European American and African American Populations. *Am J Respir Crit Care Med*. 2017;195(4):456-63.
28. Afshar M, Press VG, Robison RG, et al. A computable phenotype for asthma case identification in adult and pediatric patients: External validation in the Chicago Area Patient-Outcomes Research Network (CAPriCORN). *J Asthma*. 2017:1-8.
29. Hripcsak G, Ryan PB, Duke JD, et al. Characterizing treatment pathways at scale using the OHDSI network. *Proc Natl Acad Sci U S A*. 2016;113(27):7329-36.

FIGURES

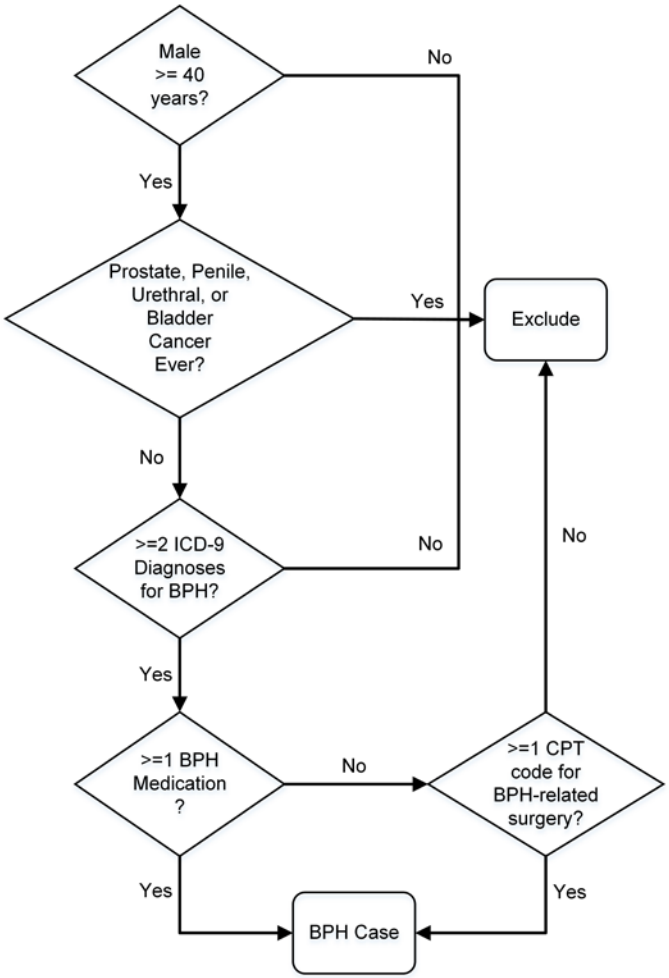
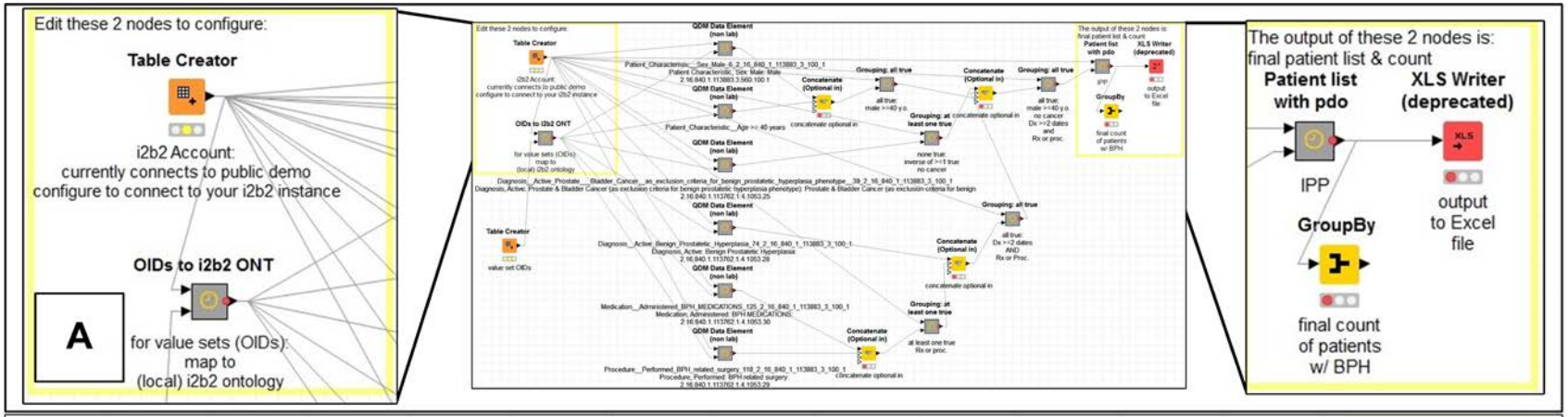


Figure 1: BPH case algorithm. ICD = International Classification of Diseases, CPT = Current Procedural Terminology: ICD and CPT codes available in the Value Sets posted at: https://github.com/PheMA/bph-use-case.


Edit these 2 nodes to configure:
Table Creator
i2b2 Account:
currently connects to public demo
configure to connect to your i2b2 instance
OIDs to i2b2 ONT
for value sets (OIDs):
map to
(local) i2b2 ontology
A
The output of these 2 nodes is:
final patient list & count
Patient list
with pdo
XLS Writer
(deprecated)
IPP
output
to Excel
file
GroupBy
final count
of patients
w/ BPH

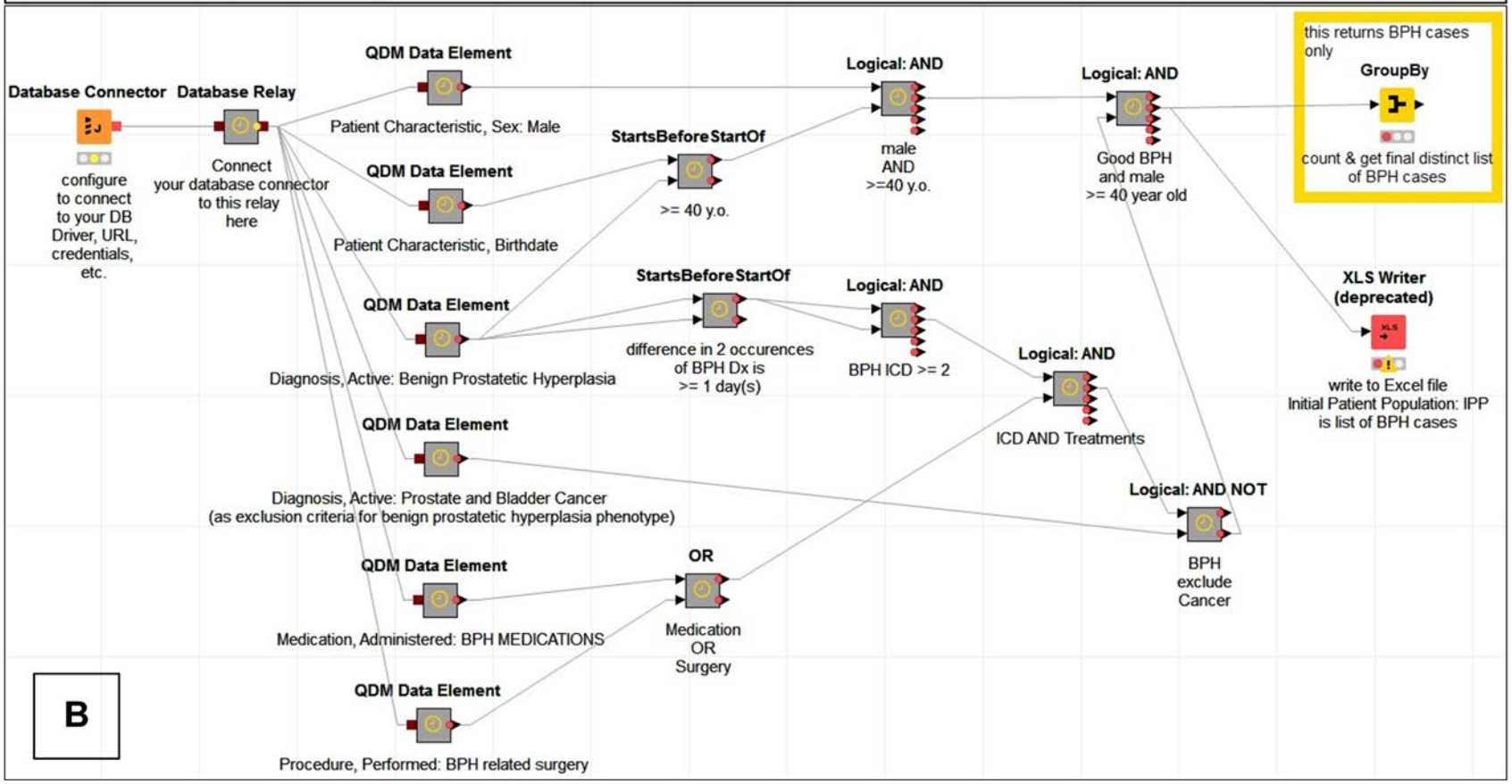

Database Connector
configure
to connect
to your DB
Driver, URL,
credentials,
etc.
Database Relay
Connect
your database connector
to this relay
here
QDM Data Element
Patient Characteristic, Sex: Male
QDM Data Element
Patient Characteristic, Birthdate
StartsBeforeStartOf
>= 40 y.o.
Logical: AND
male
AND
>=40 y.o.
Logical: AND
Good BPH
and male
>= 40 year old
this returns BPH cases
only
GroupBy
count & get final distinct list
of BPH cases
QDM Data Element
Diagnosis, Active: Benign Prostatetic Hyperplasia
StartsBeforeStartOf
difference in 2 occurences
of BPH Dx is
>= 1 day(s)
Logical: AND
BPH ICD >= 2
Logical: AND
ICD AND Treatments
XLS Writer
(deprecated)
write to Excel file
Initial Patient Population: IPP
is list of BPH cases
QDM Data Element
Diagnosis, Active: Prostate and Bladder Cancer
(as exclusion criteria for benign prostatetic hyperplasia phenotype)
Logical: AND NOT
BPH
exclude
Cancer
QDM Data Element
Medication, Administered: BPH MEDICATIONS
OR
Medication
OR
Surgery
QDM Data Element
Procedure, Performed: BPH related surgery
B

Figure 2: KNIME workflows that read data from either an i2b2 instance (A), or an LDW (B), and execute the BPH case algorithm. After a user completes configurations specific to their site within these workflows, including database connection details (server address, username, password, etc.) and any necessary data customization, the user executes the entire KNIME workflow in one step. Upon execution, each QDM Data Element node reads in the i2b2, or LDW, connection details; and i2b2 ontology mapping, or LDW queries the users modified; and extracts the relevant data, after which the subsequent nodes execute the algorithm logic. On the far right of each workflow in the XLS Writer node, in which users can specify a filename to which to write the identifiers of the patients with BPH as found by the algorithm.

A: i2b2: The Table Creator node on the top left is where a user enters their i2b2 connection details. Below that node, the "OIDs to i2b2 ONT" metanode is where users make adjustments, if necessary, to the i2b2 ontology mapping. This workflow that executes against the publicly available demonstration version of i2b2 is available at: https://github.com/PheMA/bph-use-case

B: LDW: The Database Connector node on the top left is where a user enters their LDW connection details. Then, within each QDM Data Element metanode, users open a Database Table Selector node, in which the value set for that data element is available as a variable, and edit the template query in that node to query the appropriate data for that data element from their LDW (for example, edit the template query "select *diagnois_code_column* from *diagnois_table* where diagnosis in (diagnois_list_variable)" by replacing the column and table names (*in italics*) with the column and tables names in the LDW).

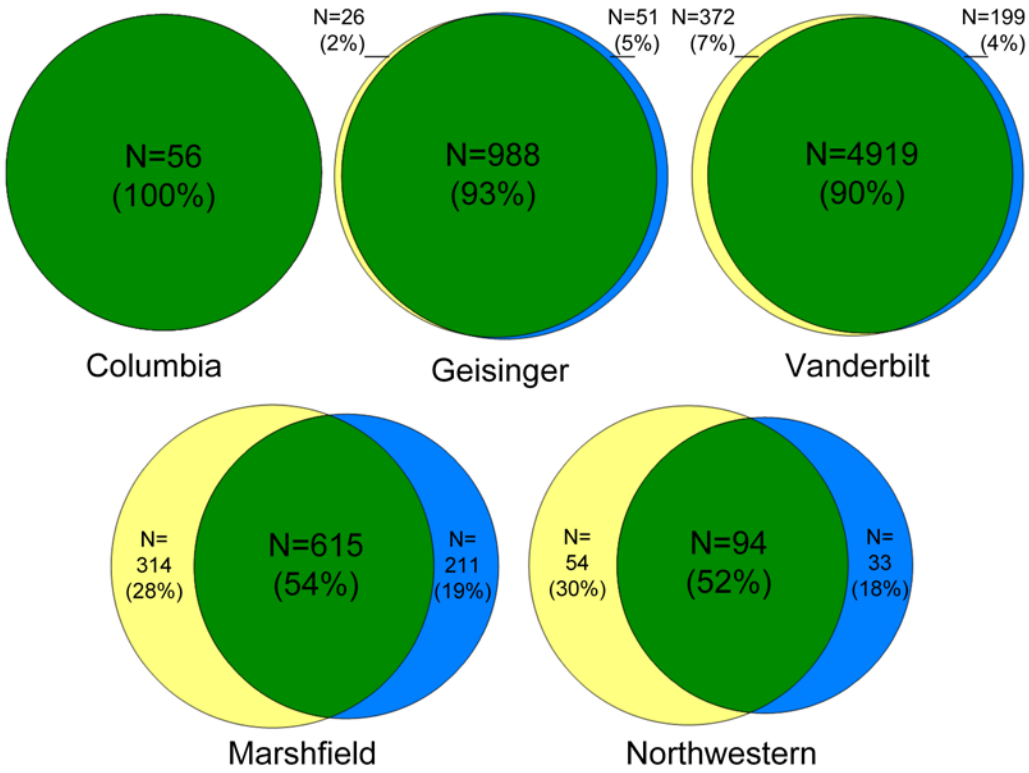


Figure 3: Comparison of eMERGE implementation to PhEMA implementation results illustrating overlap, for sites that successfully executed both the eMERGE and PhEMA implementations and thus had results to compare. Each circle in each Venn diagram is colored to represent the number of patients found by the algorithm to have BPH as follows: green depicts those found by both implementations (the overlap), yellow depicts those found only by the eMERGE implementation, and blue depicts those found only by the PhEMA implementation. Both the number (N) and percentage of patients is shown for each circle. Venn diagrams drawn by the Pacific Northwest National Laboratory's Venn Diagram Plotter, freely available from: https://omics.pnl.gov/software/venn-diagram-plotter