

Welcome to Phenotype Phebruary: Week 1 update

Patrick Ryan



type 2 diabetes mellitus

- Alzheimer disease
- heart failure
- pulmonary embolism
- type 1 diabetes mellitus
- suicidal thoughts or behavior
- deep vein thrombosis
- Long COVID
- non-small cell lung cancer (NSCLC)
- depression
- hypertension
- anxiety
- acute myocardial infarction

Guillain-Barre syndrome

- cervical cancer multiple sclerosis

Feb 1

1/2

Feb 2

- epilepsy
- kidney stones
- hemorrhagic stroke
- Systemic Lupus Erythematosus
- prostate cancer
- diabetes mellitus
 - Parkinsonism
 - autistic disorder
 - rheumatoid arthritis
 - migraine
 - hyperthyroidism
 - cardiomyopathy
 - homelessness
 - Neutropenia
- ischemic stroke Crohn's disease
- psoriasis
- anaphylaxis
- Asthma/COPD
- pregnancy
- seizure
- multiple myeloma
- atrial fibrillation
- melanoma
- acute hepatitis
- Triple Negative Breast Cancer
- acute hepatic failure
- attention deficit hyperactivity disorder
- ulcerative colitis
- bipolar disease
- peripheral artery disease
- gastrointestinal bleeding
- hypoglycemia
- pulmonary arterial hypertension
- hepatic cirrhosis
- NASH (Non-Alcoholic SteatoHepatitis)
- Acute Kidney Injury

Welcome to Phenotype Phebruary!

General



Patrick_Ryan 10

7d

Team:

It's finally arrived. That wonderful month when you can put all your troubles aside, cast off those New Year's resolutions you've already failed at, enjoy the freezing cold Northeastern US weather or the Australian heat, and JUST FOCUS ON PHENOTYPING!

28 days, 28 phenotypes. That's our target for OHDSI in 2022. Are you ready?

For those who missed it, our OHDSI community call recording is here 4 where I tried to provide a little background and motivation for this big community push together.

But to summarize it here: phenotypes are the foundational element in almost every real-world analysis we do in OHDSI, they are the natural bridge between our standardized data (the OMOP CDM) and our standardized analytics (such as ATLAS and the HADES packages). The reliability of the evidence we generate often lives and dies by the quality of the phenotypes that we use as inputs of indications, exposures, outcomes, and other features that we put into our analyses. And yet, across the broader research enterprise, the science of phenotype development and evaluation is relatively immature. The world doesn't yet have consensus best practices to design phenotypes, doesn't have agreed standardized tools to build phenotypes, doesn't have consistent, reproducible methods to evaluate phenotypes. Our phenotypes are fraught with substantial measurement error; we know we likely have suboptimal sensitivity, specificity, and positive predictive value, yet we don't consistently estimate the measurement error and even more rarely integrate measurement error into our analyses. No largescale regression or fancy deep learning model is sufficient to solidify the house of cards that our analyses rest upon if we have suspect phenotypes.

7d ago

- HIV





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Phenotype Phebruary Daily Updates

"Phenotype Phebruary" is a community-wide initiative to both develop and evaluate phenotypes for health outcomes that could be investigated by the community. Patrick Ryan introduced this initiative in both <u>a video</u> <u>presentation</u> and <u>a forum post</u>, and each of the conversations around the "28 phenotypes for 28 days" are being held within the OHDSI forums.

This page will provide direct links to each forum post, which is where conversations around each specific phenotype should be held.

Please be active in these discussions. What ways can you contribute?

1. Join the conversation

- · Discussions will be here on forums.ohdsi.org
- Each day will be a new thread
- Ex: Look for: "Phenotype Phebruary Day 1 Type 2 diabetes mellitus"
- · Explore the definitions and review the results provided
- · Reply with your thoughts, reflections, insights and question

28 Days, 28 Phenotypes



Join The Conversations

https://ohdsi.org/phenotype-phebruary/



The journey to evidence



Engineering open science systems that build trust into the real-world evidence generation and dissemination process



Measurable operating characteristics of system performance

A phenotype development and evaluation workflow





OHDSI open-source community tools to support phenotype development and evaluation process



ATLAS

- Cohort Definitions to design a rule-based cohort definition
- Profiles to review individual cases
- CapR cohort definition application programming in R, to design rule-based cohort definitions consistent with CIRCE JSON specifications
- PHOEBE to develop and evaluate a conceptset by exploring the OHDSI vocabularies for recommend candidate concepts
- APHRODITE to develop a probabilistic phenotype by training a prediction model using noisy labels
- CohortDiagnostics to evaluate phenotype algorithms using population-level characterization to identify sensitivity/specificity errors and index date misspecification
- PheValuator to evaluate a phenotype algorithm (estimate sensitivity/specificity/PPV) by training a prediction model and creating a probabilistic reference standard



How can you get involved in Phenotype Phebruary?

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 - Each day will be a new thread, all threads available via: <u>https://ohdsi.org/phenotype-phebruary/</u>
 - Explore the definitions and review the results provided
 - Reply with your thoughts, reflections, insights and questions
- Evaluate the cohort definitions in your data!
 - Execute cohort definitions and CohortDiagnostics in your CDM
 - Share insights you learn from your data on the forums
 - Share results to compile across the network on <u>data.ohdsi.org</u>
- Lead a discussion!
 - 28 days, 28 phenotypes, lots of opportunities to lead
 - I have kicked off the discussion for the first 7 days, but if others would like to similarly lead a phenotype development and evaluation activity, contact <u>ryan@ohdsi.org</u> or chat with me in OHDSI MSTeams, tell me your desired phenotype target and calendar date you want to commit to



Phenotype Phebruary resources

- <u>https://atlas-phenotype.ohdsi.org/</u>
 - ATLAS instance for OHDSI Phenotype Development WG to share cohort definitions
 - Want to get read access to this ATLAS instance?
 Fill out form here: <u>https://forms.gle/6fxcZFyufhL39pLj7</u>
- https://data.ohdsi.org/phenotypePhebruary/
 - CohortDiagnostics instance that we'll be results each day from Phenotype Phebruary evaluations
- <u>https://github.com/ohdsi-studies/PhenotypePhebruary</u>
 - Git repository where we can share code to run CohortDiagnostics
- Phenotype Development and Evaluation WG



Phenotype Phebruary

February 2022: Every day, a new phenotype will be developed and evaluated following OHDSI best practices

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
	1 Type 2 Diabetes Mellitus	2 Type 1 Diabetes Mellitus	3 Atrial Fibrillation	4 Multiple myeloma	5 Alzheimer's disease	6 Hemorrhagic events
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14 Hypertension Gowtham Rao	15 Acute myocardial infarction Gowtham Rao	16 Heart failure Gowtham Rao	17 Cardiomyopathy Gowtham Rao	18 Multiple sclerosis Azza Shoaibi	19	20
21 Prostate cancer Asieh Golozar	22 HIV Rupa Makadia	23	24	25 COVID-19 subtypes Tiffany Callahan, Juan Banda	26 Non-small-cell lung cancer Asieh Golozar	27 Drug-induced liver injury Anna Ostropolets
28	Date tbd Parkinson Allan Wu					

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Phenotype Phebruary Day 1 – Type 2 diabetes mellitus 🖋

General

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Patrick_Ryan 0	6d 🖌
Today, we'll be using OHDSI tools to develop and evaluate cohort definitions for the phenotype target Type 2 diabetes mellitus (T2DM).	et of Feb 1
Clinical description:	Feb 2
The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" is a tremendous resource to learn more about diabetes for those interested. It classifies diabetes into "the following general categories:	
 Type 1 diabetes (due to autoimmuneb-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood) Type 2 diabetes (due to a progressive loss of adequate b-cell insulin secretion frequently on th background of insulin resistance) Specific types of diabetes due to other causes, e.g.,monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancrea (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation) Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnance that was not clearly overt diabetes prior to gestation)" 	ne as h y 1d ago
It provides objective diagnostic criteria based on readily-accessible laboratory measures used in rour practice. "Diabetes can be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) value or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance (OGTT), or A1C criteria"	tine test
The epidemiology and disease natural history of T2DM has been extensively characterized in the literature. Common symptoms of T2DM onset include thirst, frequent urination, weight loss. Common	1

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literature. Common symptoms of T2DM onset include thirst, frequent urination, weight loss. Common 'risk factors' include age, obesity, hypertension and hyperlipidemia. Management of T2DM can include lifestyle modifications, including diet and exercise, as well as pharmacologic treatment (with notable drugs including metformin, Sulfonylureas, Sodium Glucose Co-Transporter 2 (SGLT2) inhibitors, Glucagon-like Peptide-1 Receptor Agonists (GLP1RA), Dipeptidyl peptidase-4 inhibitor (DPP4i), Thiazolidinediones, and insulin). Long-term complications associated ofT2DM can include cardiovascular events (ischemic heart disease, stroke), diabetic retinopathy, kidney failure, and amputation. The incidence of T2DM has been increasing over time. Current prevalence estimates of



🔀 OHDSI



Phenotype Phebruary Day 2 - Type 1 diabetes mellitus and

Gene	ral
P	Patrick_Ryan V
	Welcome everyone to Day 2 of Phenotype Phebruary! I hope you enjoyed reading the kick-off to the discussion of phenotyping Type 2 Diabetes Mellitus on Day 1 3, and encourage you to join that conservation. Meanwhile, here, I hope to stimulate another discussion, this one on Type 1 Diabetes Mellitus (T1DM).

Now admittedly, I wasn't planning to consider T1DM as a phenotype to work through during the month, because I thought it might be too close in spirit to T2DM. However, the community spoke loudly in their voting, with 20 individuals asking to explore T1DM, putting it in the top 5 of desired targets, so here we are.

And since we did T2DM yesterday, I figured today's a good opportunity stay in this related space, but highlight some different insights and observations that arise from going through the OHDSI phentoype development and evaluation process.

Clinical description:

As with T2DM, we can look to the American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" to provide a helpful frame of reference for the disease. ADA classifies diabetes into "the following general categories:

- Type 1 diabetes (due to autoimmuneb-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood)
- · Type 2 diabetes (due to a progressive loss of adequate b-cell insulin secretion frequently on the background of insulin resistance)
- Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)
- · Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)"

19h ago

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Feb 2

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Feb 3

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Here, I find the ADA's discussion about the evolving landscape of T1DM and T2DM guite informative:





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Phenotype Phebruary Day 3 - Atrial Fibrillation &

General

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Patrick_Ryan	F
Today, I'd like to a little side step from the problem of creating phenotypes de novo, and talk about how to try to implement a phenotype algorithm using OHDSI tools based on an existing description from some external material, just as a publication. I'll use the phenotype of Atrial Fibrillation to demonstrate some tips and tricks, but I hope you'll see that the steps I'll follow here are completely transportable to whatever phenotype you may want to be working on.	Feb 4 1 / 5 Feb 4
Clinical description:	
Atrial fibrillation (AFib) is an abnormal heart rhythm, often with irregular beats in the atrial chamber. CDC has a nice animated gif to illustrate what this means: Atrial Fibrillation cdc.gov 1. Initial symptoms of AFib may include feeling of irregular heartbeat or palpitations, lightheadedness, fatigue, dyspnea, and chest pain. AFib is frequently comorbid with other cardiovascular conditions, such as hypertension, coronary artery disease, and pericarditis. Patients with AFib are at higher risk of cardiovascular complications, including heart failure and ischemic stroke. Afib is most commonly diagnosed with electrocardiogram, though echocardiogram can also be used to evaluate Afib and valvular defects. AFib can be classified as 'first detected', 'paroxysmal', 'persistent', 'longstanding persistent', and 'permanent' based on the frequency and duration of abnormal heartbeat episodes.	2d ago
and anticoagulants (such as warfarin, heparin, or a direct oral anticoagulant (DOAC) such as apixaban,	
rivaroxaban, and dabigatran). Other treatments can include electrical cardioversion and catheter or	*
surgical ablation. AFib is more common in men than women, and the risk of AFib increases with age.	

** Phenotype development: **

AFib is a common target for investigation in observational databases, both as a disease that impacts future outcomes and also as an indication for various treatments that are regularly evaluated for comparative effectiveness and safety.

As a case in point, just PubMed ""atrial fibrillation" AND ("claims" OR "electronic health records")" and you'll see >1,000 articles! You'll find many recent observational studies in high-profile journals. Articles like Ray et al, "Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Patients With Atrial Fibrillation", in JAMA 1 in Dec2021 (which seems like a nice target for an OHDSI replication, wink wink @agolozar). Or Kim et al, " Machine Learning Methodologies for Prediction of Phythm Control Strategy in Patients Diagnaged With Atrial Fibrillation".



🔀 OHDSI



Phenotype Phebruary Day 4- Multiple Myeloma 🖋

General

P	Patrick_Ryan 0	1 🖋 3d	F
<u> </u>	Team:		Feb 5
	Welcome to Phenotype Phebruary Day 4! We've discuss phenotyping metabolic diseases T1DM) and a cardiovascular disease (AFib), so let's turn our attention to a different diseas a particularly active focus for many community collaborators - oncology. OHDSI's Oncolo has made good progress in thinking about advances in the OMOP CDM and OHDSI voca accommodate the study of cancers and their treatments. Another key opportunity, that I k @agolozar is quite keen to lead within the Oncology WG, is developing phenotype algor cancer target, and evaluating those algorithms across a diverse array of databases that co potentially be used to generate evidence, including administrative claims, electronic healt specialty oncology EHRs, and cancer registries. Phenotype Phebruary seems the perfect community collaboration toward this objective, starting today with Multiple Myeloma.	s (T2DM and ase area that is agy workgroup abularies to mow rithms for each could th records, ct time to get	1/8 Feb 5
	Clinical description:		
	Multiple myeloma is a type of blood cancer that affects plasma cells. Malignant white blood develop in bone marrow, suppressing healthy plasma cells that produce antibodies again Malignant plasma cells produce M protein, which can cause tumors, kidney damage, bon and impaired immune function. They also cause decreased production of red blood cells which can result in anemia and bleeding.	od cells ist infection. ne destruction and platelets,	22h ago
	Multiple myeloma is diagnosed based on plasmacytoma identified on biopsy, >30% malig cells in bone marrow aspiration, evaluated levels of M protein from protein electrophoresi or urine, osteolytic lesions observed on imaging, and IgG or IgA antibody levels in the blo diagnostics tests may include measurement of Beta2-microglobulin level. Management of myeloma typically requires pharmacologic treatment with proteasome inhibitors (including carfilzomib, ixazomib), immunomodulatory drugs (like lenalidomide, pomalidomide, thalid steroids (dexamethasone, prednisone), monoclonal antibodies (such as elotuzumab, dara isatuximab, belantamab), and chemotherapy (doxorubicin, melphalan, cyclophoshamide, bendamsutine, vincristine). Autologous stem cell transplant may be considered for those Patients may also be treated with bisphosphonates to reduce risk of bone loss.	gnant plasma is in the blood ood. Additional of multiple g bortezomib, lomide), ratumumab, , eligible.	

Multiple myeloma is more common in men than women, more common in Black or African American than whites, more common in older ages (with most cases occurring after 40 years old)





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Phenotype Phebruary Day 5- Alzheimer's Disease 🖋

General

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5	Team:		Feb 5	
	Day 5 of Phenotype Phebruary. Still lots of methodological topics to discuss and disease areas to investigate. Today, I'll try to start a conversation of the phenotype that was most highly voted on acro our community: Alzheimer's disease.	OSS	1/1 Feb 6	5
	Clinical description:			
	Alzheimer's disease is a progressive neurodegenerative disorder and the most common cause of dementia (loss of cognitive functions interfering with daily activities), representing 60-80% of cases (according to Alzheimer's Association). Initial symptoms of Alzheimer's disease may be short-term memory loss and other difficulties associated with mild cognitive impairment, such as word-finding, visual/spatial issues, and general confusion. Diagnosis of Alzheimer's disease may involve neurolog exam, including brain MRI or CT scans, to identify other potential causes of dementia other than Alzheimer's, and mental cognitive status tests. Drugs approved for use in Alzheimer's disease inclue cholinesterase inhibitors (such as donepezil, galantamine, or rivastigmine) and memantine, which a primarily aimed at treating cognitive symptoms. In 2021, aducanumab was approved by US FDA on basis of clinical trial data suggesting reduction of amyloid beta plaque. Alzheimer's disease risk increases with age, with most cases detected after 65 years old. Prevalence of AD is higher in fema than males, though that is attenuated by female longer life span. It is one of leading causes of death globally, and second-leading cause in high-income countries (WHO).	jical de re the lles	2d ago	1
	Phenotype development:			

I've mentioned in prior posts that a valuable starting point for phenotype development can be the published literature, and I've shown how you - provided that a journal article supplied enough details - you can replicate their algorithms using OHDSI tools. But I want to take a digression here for a little rant: if observational researchers all need to develop phenotypes to conduct our analyses and should all review prior literature as part of our research process, then why is so hard to search for publications of observational research and extract out the phenotypes that were previously used? If phenotypes are so central to the integrity of our research, then as a research community, why do we accept short freetext descriptions of phenotypes in manuscripts, sometimes without list of codes and often without a complete specification of the logic that was used to implement them? And for those of us promoting increased transparency, when we try to add additional detail in supplemental materials, why do we often format it in ways that make it painful for others to re-use without extensive manual curation? When I





Phenotype Phebruary Day 6- Hemorrhagic events 🖋

General

Patrick_Ryan V	1d	×
Welcome to Phenotype Phebruary Day 6!		Feb 6
Up to this point, we've discussed phenotype targets that are generally considered chror (T2DM 1, T1DM 1, AFib, multiple myeloma 1, Alzheimer's). As such, our focus has a identifying cohort entry, with the subposition that once a person enters the cohort, they health state until the end of their observation.	nic diseases been primarily on remain in that	1 / 5 Feb 7
Today, I'd like to talk about creating a cohort definition that allows for a person to enter a cohort multiple times. We'll use hemorrhagic events and bleeding-related hospitalization example. This will subsume a couple phenotypes high on the OHDSI wishlist : hemorrh gastrointestinal bleeding.	and exit the ns as our nagic stroke and	
Our motivating use case: In our AFib discussion, we noted a recent paper by Ray et al, Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Patients With Fibrillation", in JAMA 1 in Dec2021. In that study, the target and comparator population with AFib with DOAC exposure, so we should be clear how we could use our AFib coho with a new user drug cohort, and identify the patients eligible to be analyzed. That was	"Association of Atrial ns were persons ort, intersect it the easy part,	101
now we'll tackle the trickier bit: finding the outcomes for those patients. In their publicati	ion, Ray et al	18h ago
and systemic embolisms, and hemorrhagic events including hemorrhagic strokes and b hospitalizations. Today, I'll just focus on that second aspect.	pleeding-related	÷ 1
Clinical description:		
I had fun looking for a clinical definition to report here without sounding stupid: Medliner this: "Bleeding is the loss of blood". Google's healthbox provides defines bleeding (aka "the release of blood from a broken blood vessel, either inside or outside the body". Per informative.	plus gave me hemorrhage) as rhaps not terribly	
In part, its because it's an ill-specified phenotype target: hemorrhage can be the result f	from a broad	

constellation of injuries, can occur anywhere throughout the body, and can have consequences that vary from inconsequential/self-remedying to fatal. External bleeding is usually easy to detect (look for red), and if that does not resolve after a few minutes of applying pressure may require to seek medical attention. Internal bleeding may be initially asymptomatic, but initial signs can include hypotension, abnormal heart rate or breathing, drowsiness or loss of consciousness, in addition to observing blood





Phenotype Phebruary Day 7 - Neutropenia 🖋

General

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Patrick_Ryan 🖤	10h	×
Team:		Feb 8
Can you believe that the end of week 1 of Phenotype Phebruary is already here?!? Time flies when you're having fun.		1 / 1 Feb 8
In the first six days, I tried to initiate conversations around phenotyping diseases that were primarily defined by condition occurrence records (T2DM, T1DM, AFib, multiple myeloma, Alzheimers, bleed But there continues to be a lot of interest in our community in using measurement values as part of phenotyping process. So, today, let's talk about Neutropenia.	ing). the	
Clinical description:		
Neutropenia is abnormally low count of neutrophils in the blood. Neutrophils are the primary circula white blood cells and function as part of the immune system to respond to inflammation and bacter infections. So, persons with neutropenia are are increased risk of infection. While neutropenia itsel be asymptomatic, symptoms often manifest as a result of an infection, and can include fever, pain is swallowing or gums, or skin abcesses. Neutropenia can be congenital or acquired, and acute or chronic, and is known to be associated with various conditions and attributed to drug exposure. When the statement of the	ting al can n	10h ago
neutropenia is specifically referred to decreased neutrophils, other conditions are known to observe	2	
neutropenia in conjunction with other phenomena. Pancytopenia is decrease in red blood cells, wh blood cells, and platelets. Leukopenia is low white blood cells of any time, which generally is inclus neutropenia.	te ive of	÷ 1

Neutropenia can be diagnosed by measurement of neutrophils. One diagnostic criteria for severe neutropenia is absolute neutrophil count (ANC) < 500 cells per microliter of blood, while moderate neutropenia can be identified by ANC between 500-1000 cells per microliter, and mild neutropenia is classified as ANC between 1000 - 1500 cells per microliter. Severe neutropenia poses the greater infection risk, and is often where medical attention is recommended. However, since severe neutropenia is rare, it can be difficult to identify and classification, even with ease of measurement from a complete blood count test. Additional bone marrow biopsy may be required as a diagnostic procedure.

Treatment for neutropenia can include granulocyte colony stimulating factor (G-CSF), including filgrastim, and antibiotics to manage bacterial infections.



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Phenotype Phebruary

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28	Date tbd Parkinson Allan Wu					