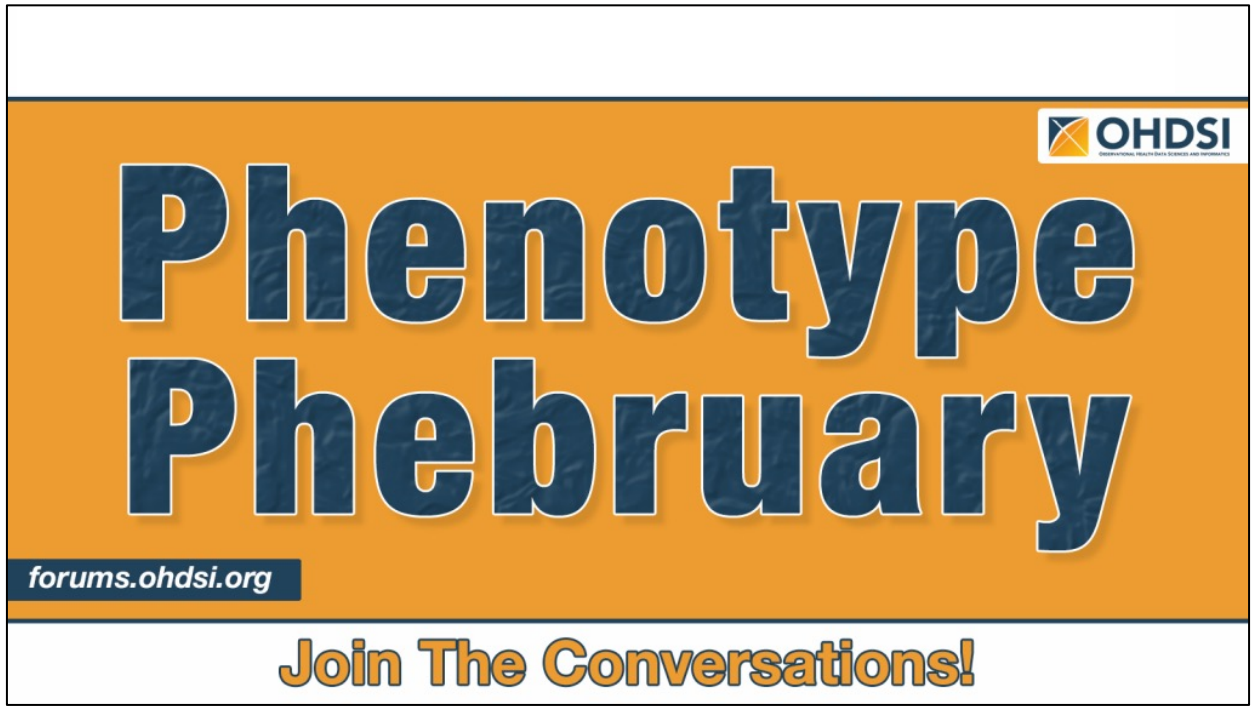
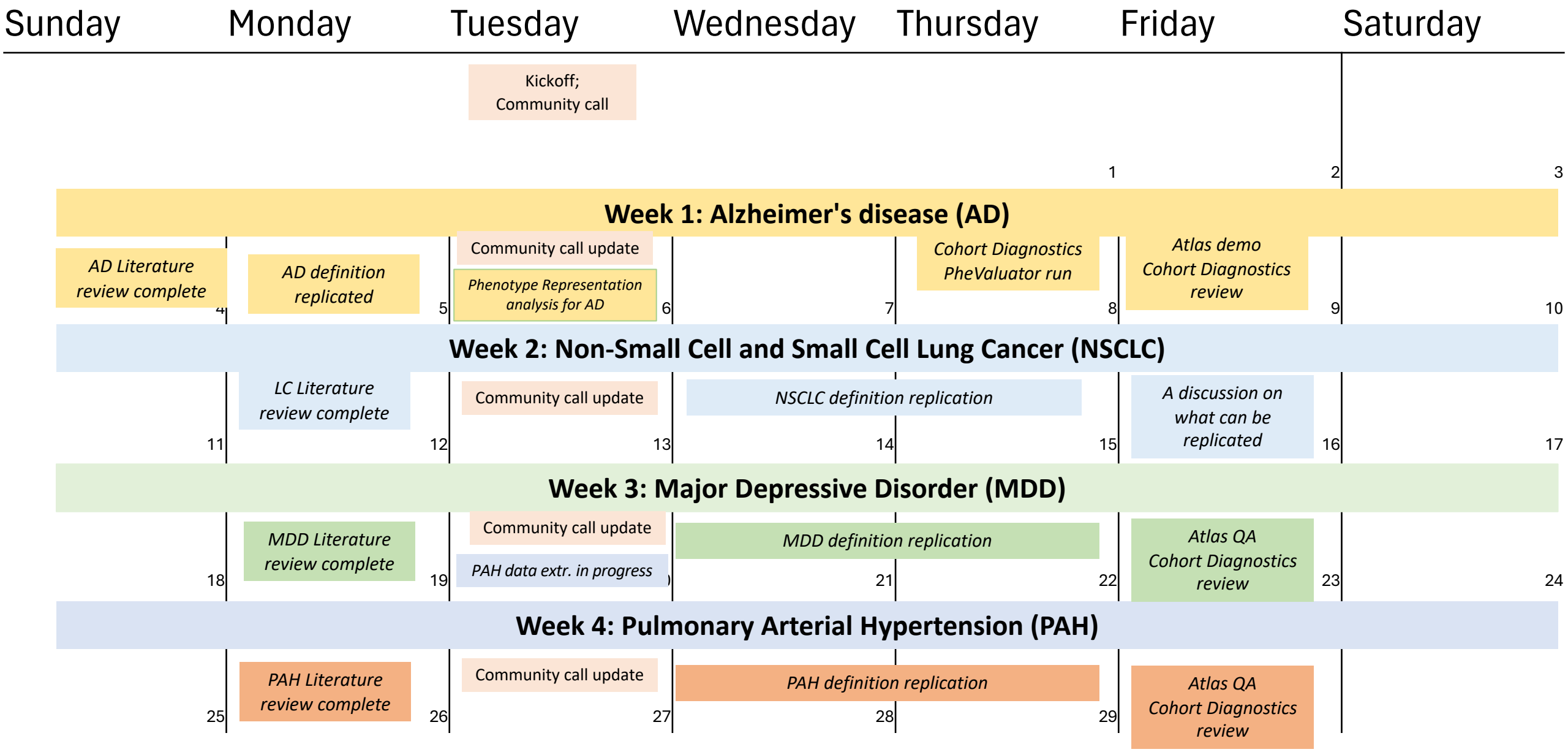
2024 Edition



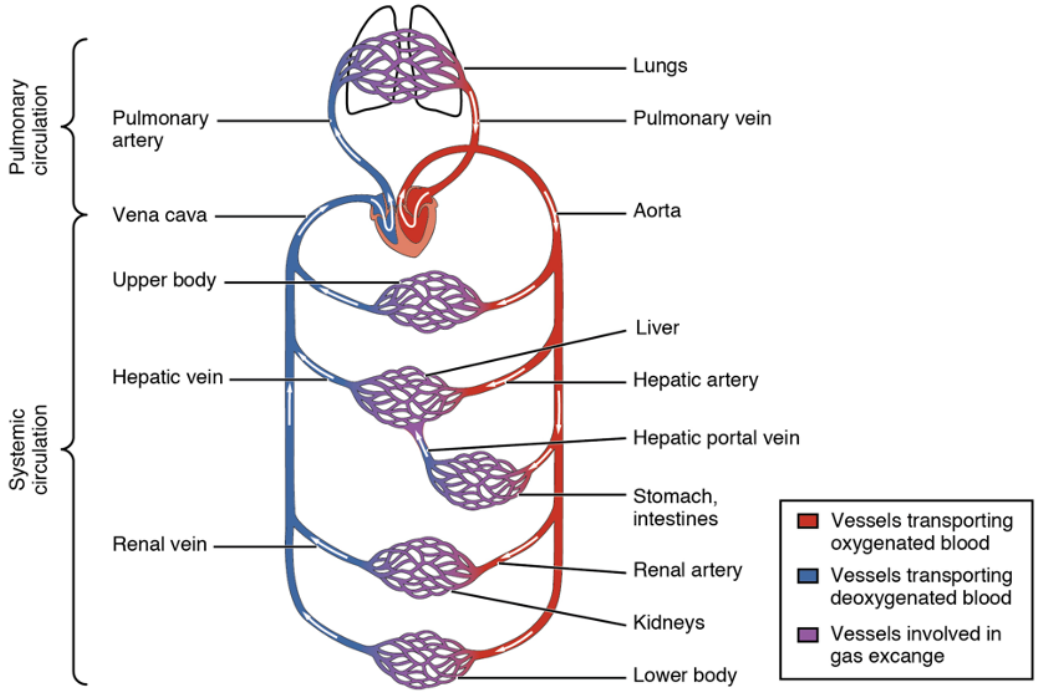
February 27th, 2024

Community call update

Phenotype Phebruary 2024 Calendar

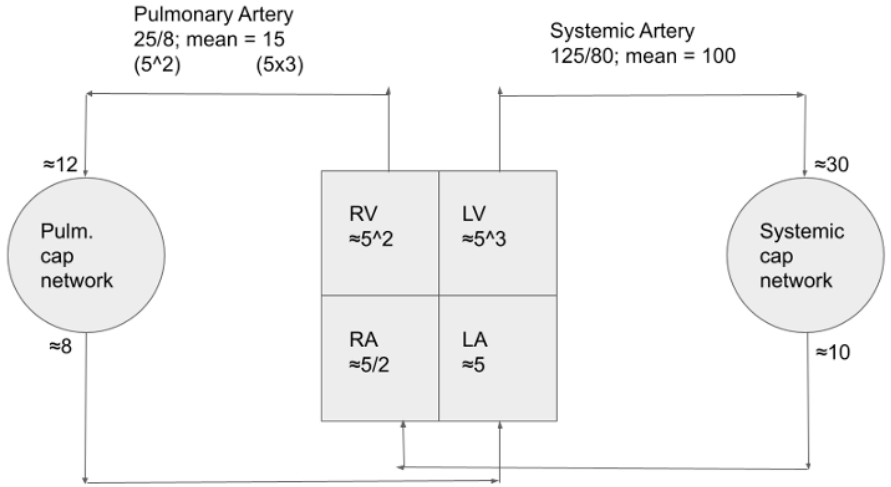


Pulmonary Hypertension & Pulmonary Arterial Hypertension



https://en.wikipedia.org/wiki/Capillary

Pulmonary Hypertension:
Mean Pulmonary Artery Pressure > 20mmHg (normal 8-20)



https://forums.ohdsi.org/t/putting-the-ph-in-phenotype-phebraury-day-20/15983

Pulmonary Arterial Hypertension: Diagnosis

- **Group 1 – Pulmonary Arterial Hypertension**
  - **Primary / idiopathic**
  - **Secondary to CTDz, drugs, toxins, infections..**
- Group 2 – PH Due to Left Heart Disease
- Group 3 – PH due to Chronic Lung Disease and/or hypoxemia
- Group 4 – PH due to Pulmonary arterial obstructions
  - Chronic Thromboembolic Pulmonary Hypertension, CTEPH)
- Group 5 – Unclear, multifactorial mechanisms

Precapillary: Blue

(mostly) Post capillary: Red

Mixed: Purple

ICD-9 Code	Definition	ICD-10 Code	Definition
416.0	Chronic pulmonary heart disease	I27.0	Primary pulmonary hypertension
416.2	Chronic pulmonary embolism	I27.2	Other secondary pulmonary hypertension
416.8	Other chronic pulmonary heart diseases		
416.9	Chronic pulmonary heart disease, unspecified		

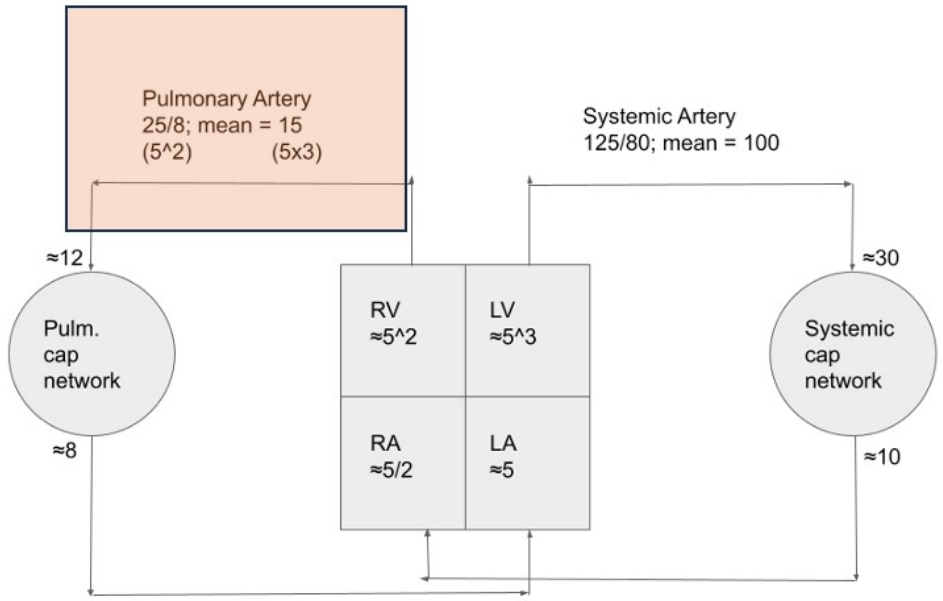
ICD-9 and ICD-10 Coding systems do not reflect the Clinical Classification of PH

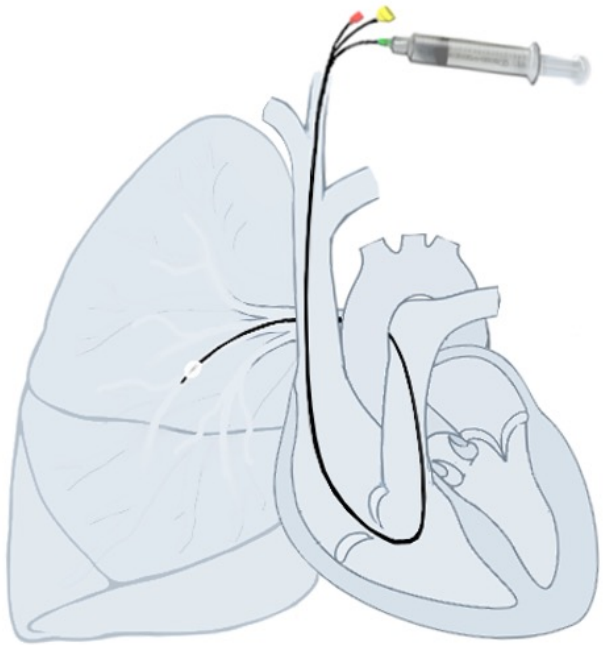
PVRI RWE Working Group; Jan 31 2024; with permission

Pulmonary Arterial Hypertension: Diagnosis

Pulmonary Hypertension: Mean PAP > 20mmHg

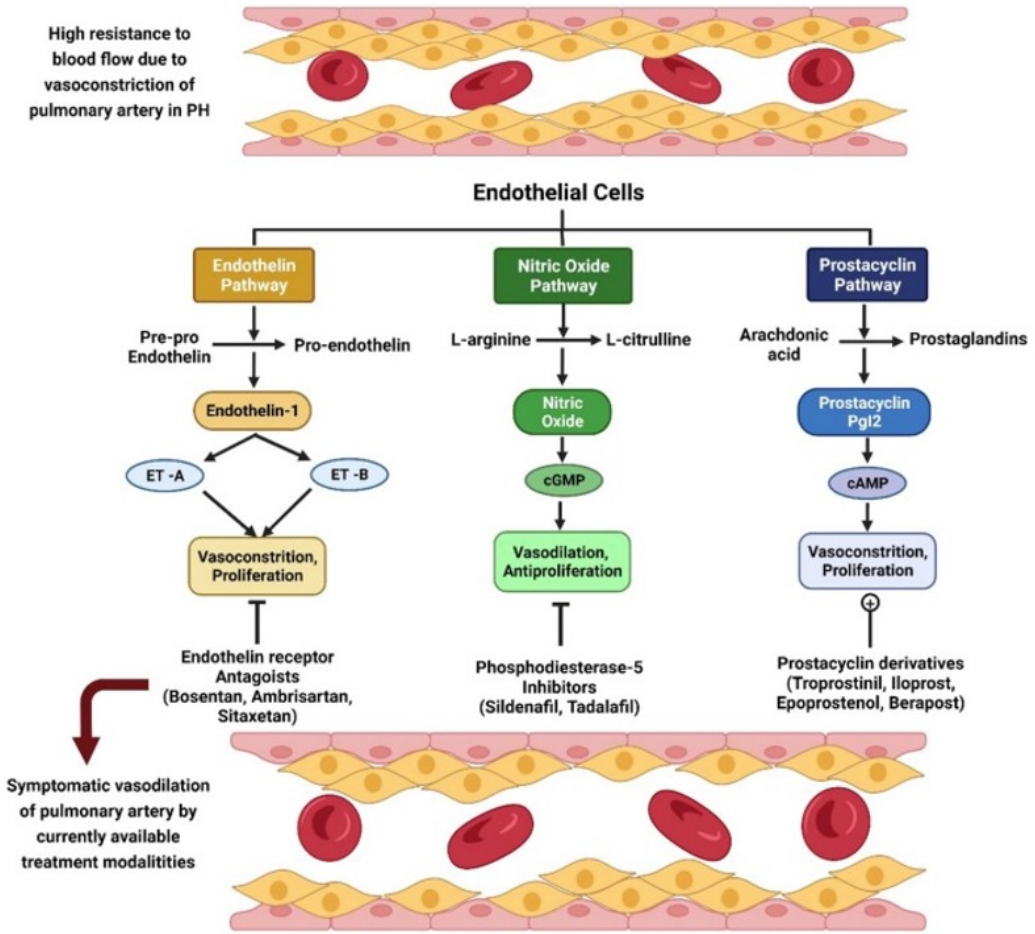
Pulmonary Arterial Hypertension: Mean PAP > 20mmHg &
wedge Pressure < 15 mmHg &
PVR > 2 Wood Units





https://en.wikipedia.org/wiki/Cardiac_catheterization

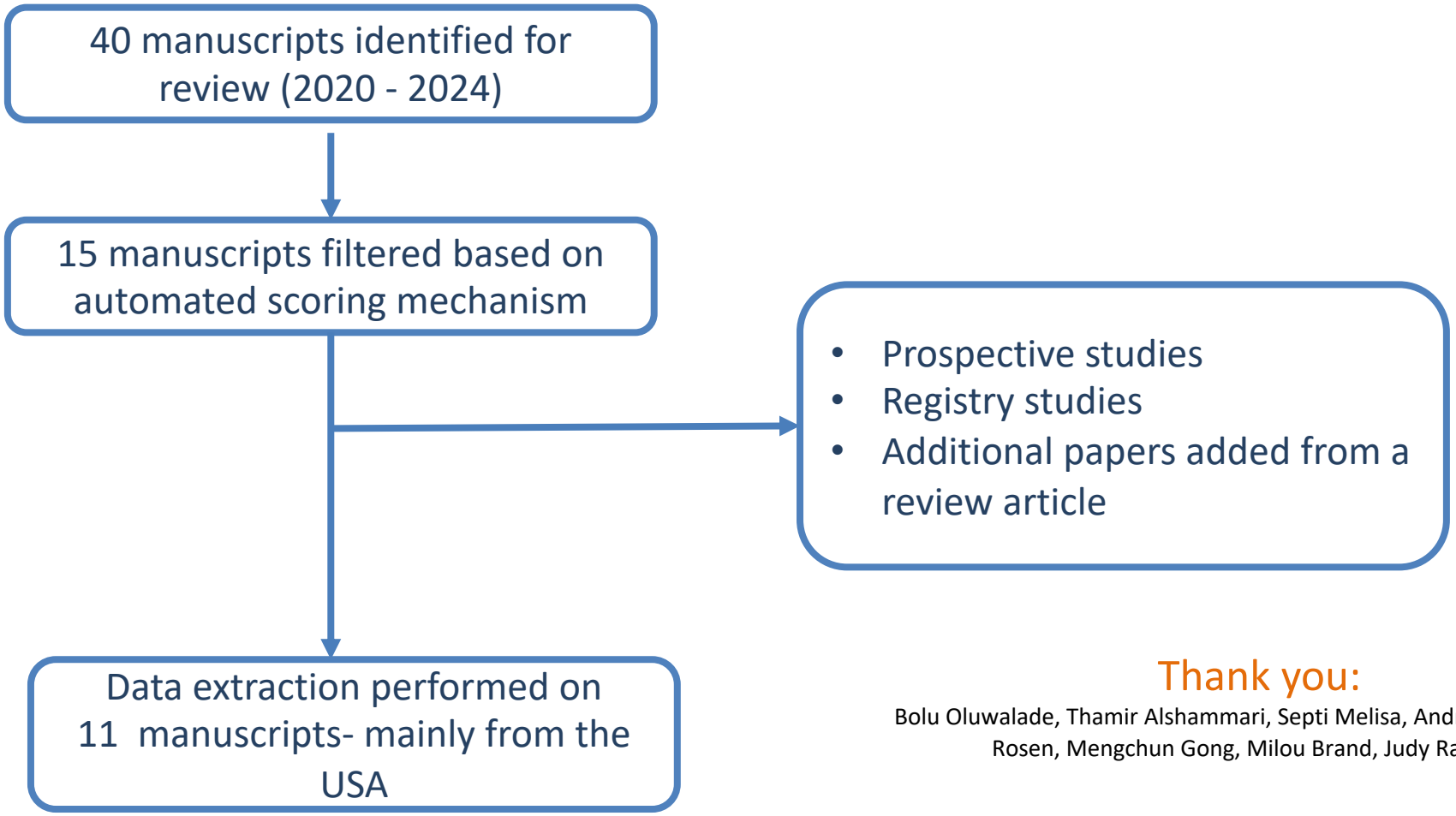
Pulmonary Arterial Hypertension: Therapy



https://www.sciencedirect.com/science/article/pii/S0378517322003477?via%3Dihub (Creative Commons)

- PAH patients have:
  - Elevated levels of Endothelin-1 (vasoconstrictor)
    - **Endothelin Receptor Antagonists**
  - Low levels of endogenous Nitrous Oxide (NO)
    - **PDE-5i ; soluble cGMP stimulators**
  - Low levels of Prostacyclin
    - **Prostacyclin Derivatives**
- Calcium Channel Blockers in NO responsive
- Anticoagulation (controversial)
- Some may be tried in other PH groups (possible elements of PAH in Group 2-5)
- Dual therapy now used in most PAH patients if diagnosed when symptomatic

What did we do?



Thank you:

Bolu Oluwalade, Thamir Alshammari, Septi Melisa, Andreas Weinberger Rosen, Mengchun Gong, Milou Brand, Judy Racoosin

Glance at phenotype definitions

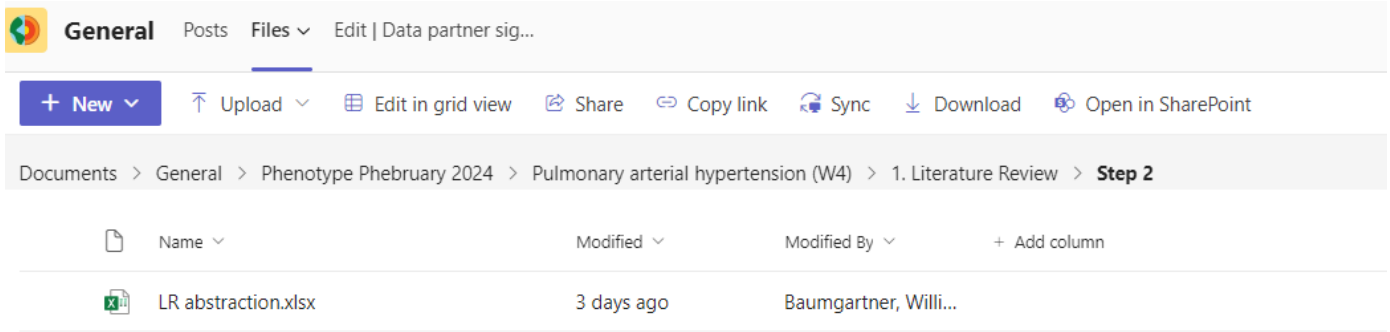
Common patterns in concept sets:

- I27.0 (Primary pulmonary hypertension) only or add
- I27.20,I27.21 (Pulmonary hypertension, unspecified, Secondary pulmonary arterial hypertension)
- and I27.89 (Other specified pulmonary heart

Common patterns in phenotype definitions:

- One or two of the diagnoses
- commonly require a treatment, with variation in the treatment list
- exclusion of differential diagnoses (chronic thromboembolic pulmonary hypertension)

- More details when we replicate the cohorts!



RESEARCH ARTICLE | Open Access

Clinical evaluation of code-based algorithms to identify patients with pulmonary arterial hypertension in healthcare databases

Eva-Maria Didden, Di Lu, Andrew Hsi, Monika Brand, Haley Hedlin, Roham T. Zamanian

First published: 08 February 2024 | https://doi.org/10.1002/pul2.12333

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Abstract

[Identifying Patients with Pulmonary Arterial Hypertension Using Administrative Claims Algorithms - PubMed (nih.gov)]

PAH Phenotype Validation

OHDSI Community Call

February 27th, 2024

Eva-Maria Didden

On behalf of the study teams:

PheValuator-based PAH phenotype validation: Viviane Sprecher, EMD, Joel Swerdel, Audrey Muller

Clinical PAH phenotype validation through database linkage: EMD, Di Lu, Andrew Hsi, Monika Brand, Haley Hedlin, Roham T. Zamanian

Background – PAH phenotype validation

Pulmonary Arterial Hypertension [PAH]:

- Subgroup of Pulmonary Hypertension [PH] with diverse etiologies.
- Rare and life-threatening, but treatable (not curable!).
- Unspecific symptoms, high misdiagnosis rates, delayed diagnosis.

The challenge: identifying PAH patients in observational healthcare databases:

- PAH diagnosis codes:
  - release of P(A)H-specific ICD codes only in Oct '17.
  - might represent a rule-out diagnosis or suspicion of the disease (i.e., PAH code used for specialist referral or PAH screening purposes).
- PAH drug codes: might be used off-label for treatment of other forms of PH.

Common solution: Well-defined temporal sequences of diagnosis, procedure, drug, and/or exclusionary codes ➔ PAH phenotype algorithms.

Objectives – PAH phenotype validation

Most recent publication*:

To demonstrate PAH phenotype validation through linkage of an EHR database with a PH-specific clinical database.

➔ see next slides

Previous PheValuator work:**

To validate PAH phenotype algorithms identified via a systematic literature search in US health insurance claims databases, using PheValuator.

*Didden EM, Lu D, Hsi A, Brand M, Hedlin H, Zamanian RT. *Clinical evaluation of code-based algorithms to identify patients with pulmonary arterial hypertension in healthcare databases.* Pulm Circ. 2024 Feb 8;14(1):e12333. doi: 10.1002/pul2.12333. PMID: 38333073; PMCID: PMC10851026.

**Sprecher VP, Didden EM, Swerdel JN, Muller A, *Evaluation of code-based algorithms to identify pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension patients in large administrative databases,* Pulm Circ 2020;10:2045894020961713

Methods – clinical PAH phenotype validation

Databases, linked through unique patient identifiers:

- Stanford Healthcare administrative EHR database ← to apply the algorithms.
- Stanford Vera Moulton Wall Center (VMWC) clinical PH database ← to perform clinical case validation and assessment of algorithm performance.

PAH phenotype algorithms for validation:

- Six published algorithms.
- Ten additional clinically meaningful algorithms.

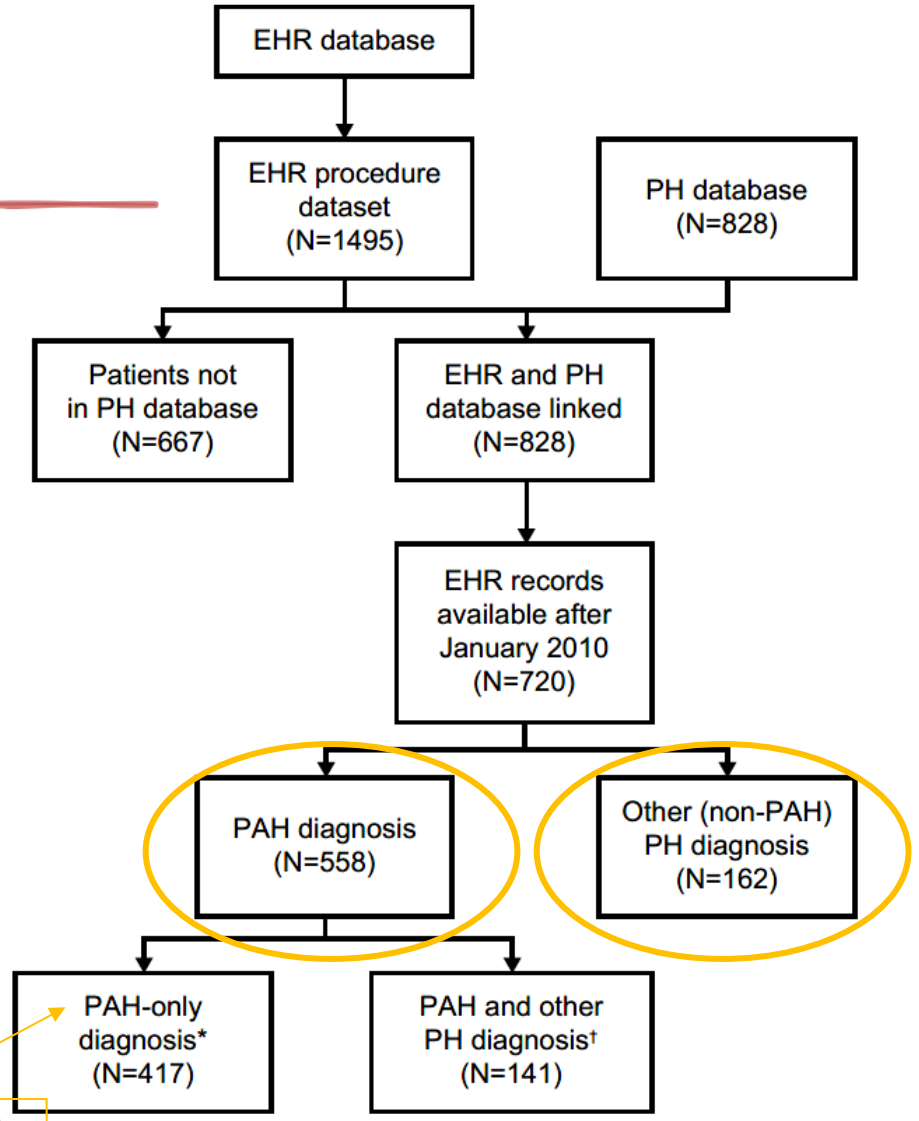
Algorithm performance metrics:

- True Positives, True Negatives, False Positives, False Negatives.
- Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV).

Patient Funnel

Eligible PH patients:

- ≥ 18 years of age,
- linkable records,
- ≥1 Right Heart Catheterization (RHC) at Stanford VMWC,
- a confirmed PH diagnosis (mean pulmonary arterial pressure ≥25 mmHg),
- ≥6 months of observation after their first RHC at Stanford VMWC (unless they died),
- in case of an early death, ≥1 visit between the first RHC and death.



*Patients with a PAH diagnosis and no PH WHO Group II–V diagnosis at any point in their medical history.

†Patients with a PAH diagnosis and a PH WHO Group II–V diagnosis at any point in their medical history.

Results:

Dx: diagnostic code;

RHC: right heart catheterization;

TTE: transthoratic echocardiography;

Rx: pharmacy claim;

Excl: exclusionary codes;

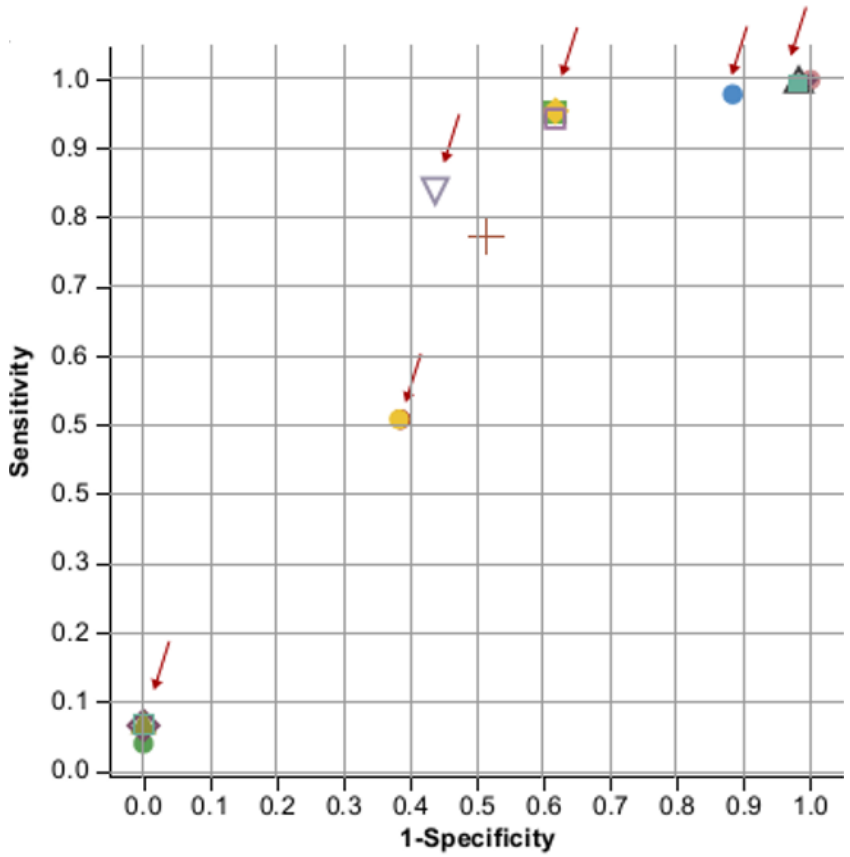
temporal component;

PMID: PubMed ID;

CI: confidence interval.

Algorithm ID / PMID	Algorithm includes: Dx	RHC/ TTE	Rx	Excl	temporal	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Published algorithms									
2 / 28678692						**1.000** (0.993, 1.000)	**0.000** (0.000, 0.000)	**0.775** (0.742, 0.805)	**0.000** (0.000, 0.000)
1 / 27851838						**0.978** (0.962, 0.988)	**0.117** (0.072, 0.177)	**0.792** (0.760, 0.822)	**0.613** (0.421, 0.781)
6 / 30421652						**0.953** (0.932, 0.969)	**0.383** (0.307, 0.462)	**0.841** (0.810, 0.869)	**0.704** (0.597, 0.797)
3 / 28762848						**0.953** (0.932, 0.969)	**0.383** (0.307, 0.462)	**0.841** (0.810, 0.869)	**0.704** (0.597, 0.797)
5 / 30566510						**0.068** (0.048, 0.092)	**1.000** (0.977, 1.000)	**1.000** (0.907, 1.000)	**0.237** (0.206, 0.271)
4 / 29485908						**0.041** (0.026, 0.061)	**1.000** (0.977, 1.000)	**1.000** (0.851, 1.000)	**0.232** (0.201, 0.265)
Additional (unpublished) algorithms									
9 / NA						**0.998** (0.990, 1.000)	**0.000** (0.000, 0.000)	**0.775** (0.742, 0.804)	**0.000** (0.000, 0.000)
7 / NA						**0.996** (0.987, 0.999)	**0.018** (0.003, 0.053)	**0.777** (0.745, 0.807)	**0.600** (0.146, 0.947)
8 / NA						**0.996** (0.987, 0.999)	**0.018** (0.003, 0.053)	**0.777** (0.745, 0.807)	**0.600** (0.146, 0.947)
10 / NA						**0.944** (0.922, 0.961)	**0.383** (0.307, 0.462)	**0.840** (0.809, 0.868)	**0.666** (0.561, 0.761)
11 / NA						**0.845** (0.813, 0.874)	**0.562** (0.481, 0.639)	**0.869** (0.837, 0.896)	**0.514** (0.438, 0.589)
12 / NA						**0.774** (0.737, 0.808)	**0.488** (0.408, 0.567)	**0.838** (0.804, 0.869)	**0.385** (0.318, 0.455)
13 / NA						**0.509** (0.466, 0.551)	**0.617** (0.537, 0.692)	**0.821** (0.776, 0.859)	**0.267** (0.223, 0.315)
13b / NA						**0.509** (0.466, 0.551)	**0.617** (0.537, 0.692)	**0.821** (0.776, 0.859)	**0.267** (0.223, 0.315)
7b / NA						**0.069** (0.050, 0.094)	**1.000** (0.977, 1.000)	**1.000** (0.909, 1.000)	**0.237** (0.206, 0.271)
9b / NA						**0.068** (0.048, 0.092)	**1.000** (0.977, 1.000)	**1.000** (0.907, 1.000)	**0.237** (0.206, 0.271)

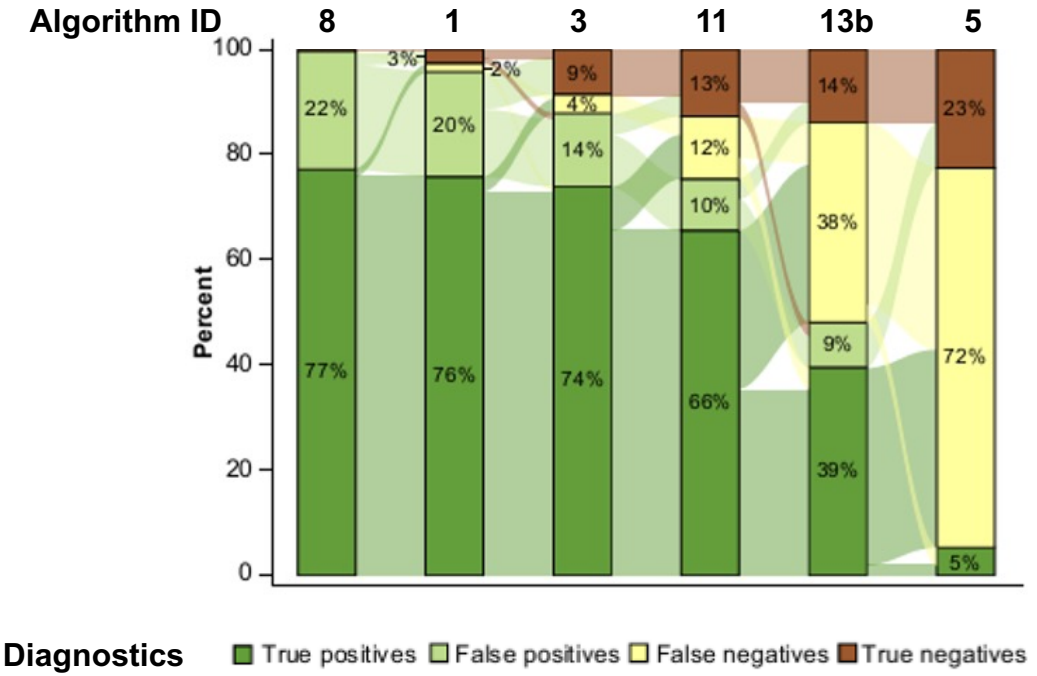
Sensitivity-Specificity Trade-Off



Algorithm ID

1 2 3 4 5 6 7 7b
8 9 9b 10 11 12 13 13b

Algorithm ID	8	1	3	11	13b	5
Dx						
RHC/TTE						
Rx						
Excl						



Diagnostics True positives False positives False negatives True negatives

Summary

There is no “best” algorithm:

- Inclusive algorithms with high sensitivity (> 0.94) are non-specific (specificity <0.40).
- Selective algorithms with high specificity (1.00) are not sensitive (sensitivity <0.10).
- Algorithms with a reasonable balance of sensitivity and specificity (both >0.50) typically consist of well-defined temporal sequences of procedure, diagnosis, and drug codes.
- In line with expert findings and recommendations for PAH algorithm development*.

Notes from additional/sensitivity analyses:

- Across all algorithms, only minor random variations in characteristics of correctly identified PAH patients.
- Same findings when excluding patients with both a PAH and a PH WHO Group II–V diagnosis from study.

* Mathai SC et al., *Identifying Patients with Pulmonary Arterial Hypertension Using Administrative Claims Algorithms*. Annals of the American Thoracic Society. 2019;16(7):797-806.

Recommendations

1. Tailor algorithm selection/design to the specific research question.
   ← Is a sensitive, specific, or balanced algorithm required?

2. Revisit research question and assess all relevant patient characteristics.
   ← Should additional selection criteria/codes be included in the algorithm?

3. Include temporal components in the algorithm, as appropriate.
   ← What should be the temporal sequence of events/codes? This can vary between regions and healthcare systems.

4. Describe your algorithm(s) in detail in your publication.

Strengths and Limitations

- **This study provides a robust case validation:** all true P(A)H patients could be classified based on RHC – the gold standard - in the clinical database.

- Stanford is a center of specialized PH care ➔ PAH prevalence may be biased among PH patients ➔ generalizability of results may be impacted.

- The team suggests performing additional case validation across databases and healthcare settings based on the presented findings.

Comparison with PheValuator study

	Clinical validation study	PheValuator study
Databases	EHRs linked to a clinical PH database	3 US claims databases (general population)
PAH prevalence in database	78% in clinical PH database	0.16%–0.87%,
Ground truth	RHC (gold standard diagnostic test)	Predictions by PheValuator mathematical models that estimated the probability of each patient having PAH
Data available	In- and outpatient information were available in the Stanford EHR database but could not be distinguished from each other ➔in-/outpatient algorithm components could not be considered	In- and outpatient information could be distinguished from each other.

Findings

Algorithm rankings by sensitivity, specificity, PPN, and NPV and overall conclusions were largely similar.

EHR, electronic health records; PAH, pulmonary arterial hypertension; RHC, right heart catheterisation.

Conclusion

Both phenotype validation studies contribute to:

- having a range of universally accepted fit-for-purpose PAH phenotype algorithms, tailored to address different types of research questions.
- informing future phenotype validation work in coded healthcare databases, especially in rare or complex diseases.

References:

- Sprecher VP, Didden EM, Swerdel JN, Muller A, *Evaluation of code-based algorithms to identify pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension patients in large administrative databases,* Pulm Circ 2020;10:2045894020961713
- Didden EM, Lu D, Hsi A, Brand M, Hedlin H, Zamanian RT. *Clinical evaluation of code-based algorithms to identify patients with pulmonary arterial hypertension in healthcare databases.* Pulm Circ. 2024 Feb 8;14(1):e12333. doi: 10.1002/pul2.12333. PMID: 38333073; PMCID: PMC10851026.
- Mathai SC et al., *Identifying Patients with Pulmonary Arterial Hypertension Using Administrative Claims Algorithms*. Annals of the American Thoracic Society. 2019;16(7):797-806.

Published algorithms validated using PheValuator and via database linkage:

1. Anand V et al., *Trends and Outcomes of Pulmonary Arterial Hypertension-Related Hospitalizations in the United States: Analysis of the Nationwide Inpatient Sample Database From 2001 Through 2012.* JAMA cardiology. 2016;1(9):1021-9.
2. Choi YM et al., *Incidence of Pulmonary Arterial Hypertension in Patients with Psoriasis: A Retrospective Cohort Study.* The Permanente journal. 2017;21:16-073.
3. Dufour R et al., *Healthcare resource utilization and costs for patients with pulmonary arterial hypertension: real-world documentation of functional class.* Journal of medical economics. 2017;20(11):1178-86.
4. Kim D et al., *Phosphodiesterase-5 Inhibitor Therapy for Pulmonary Hypertension in the United States.* Actual versus Recommended Use. Ann Am Thorac Soc. 2018;15(6):693-701.
5. Song S et al., *Demographics, treatment trends, and survival rate in incident pulmonary artery hypertension in Korea: A nationwide study based on the health insurance review and assessment service database*. PloS one. 2018;13(12):e0209148.
6. Studer S et al., *Treatment patterns, healthcare resource utilization, and healthcare costs among patients with pulmonary arterial hypertension in a real-world US database.* Pulm Circ. 2019;9(1):2045894018816294.

Next steps

- PAH cohort replication (sign up in the sheet)
- MDD cohort diagnostics review
- PAH cohort diagnostics review next Monday
- Study package (Jamie in contact with data partners)
- Open call to plan the manuscript