

# Systematic, automated screening to improve the diagnosis and management of primary aldosteronism

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# Background

- Primary aldosteronism (PA) is responsible for hypertension in ~1% of adults (5% of hypertension patients)
- PA can be cured by adrenalectomy or treated with mineralocorticoid receptor antagonists
- PA is not recognized in up to 99% of affected patients
- Endocrine Society Practice 2016 Guidelines recommend PA screening in specific subgroups of hypertension patients

# Specific Aims

- **Aim 1:**
  - Identify and characterize UPHS patients with known primary aldosteronism.
- **Aim 2:**
  - Develop an algorithm to identify UPHS patients with undiagnosed primary aldosteronism.
- **AIM 3 (*Year 2*):**
  - Prospectively implement clinical decision support to improve the diagnosis and management of primary aldosteronism.

# Clinical Impact

- **Direct patient effects:**

- Facilitate the **diagnosis of primary aldosteronism in hundreds** of UPHS patients
- Enable us to offer patients precision medical or surgical therapy
- Short-term:
  - Increase laboratory, medicine specialty, radiology, and surgical care
  - **Improve blood pressure control**
- Long-term:
  - Decrease care visits to manage poorly controlled hypertension
  - **Decrease burden of future cardiovascular, cerebrovascular, and renal morbidity**

- **Health system:**

- Strengthen offering of **precision hypertension and cardiovascular care**

- **Infrastructure:**

- Build resources and methods for **advanced clinical decision support**, including recommending diagnoses and helping to ensure accurate testing and interpretation

# Team & Resources

- Clinical development:
  - Julia Kharlip (Endocrine), Debbie Cohen (Renal), Scott Trerotola (Interventional Radiology), Douglas Fraker (Endocrine Surgery)
- Statistical design and implementation:
  - Jinbo Chen (Biostats)
- Informatics:
  - Data Analytics Center Penn Data Store and Epic Clarity, IBI Clinical Informatics Research Core, David Birtwell (TURBO), Linguamatics
- Clinical implementation:
  - Craig Umscheid (Medicine), PM Predictive Healthcare Penn Signals
- Biomedicine:
  - PM BioBank and Dan Rader, Scott Damrauer, JoEllen Weaver

# Aim 1: Identify UPHS patients with known PA

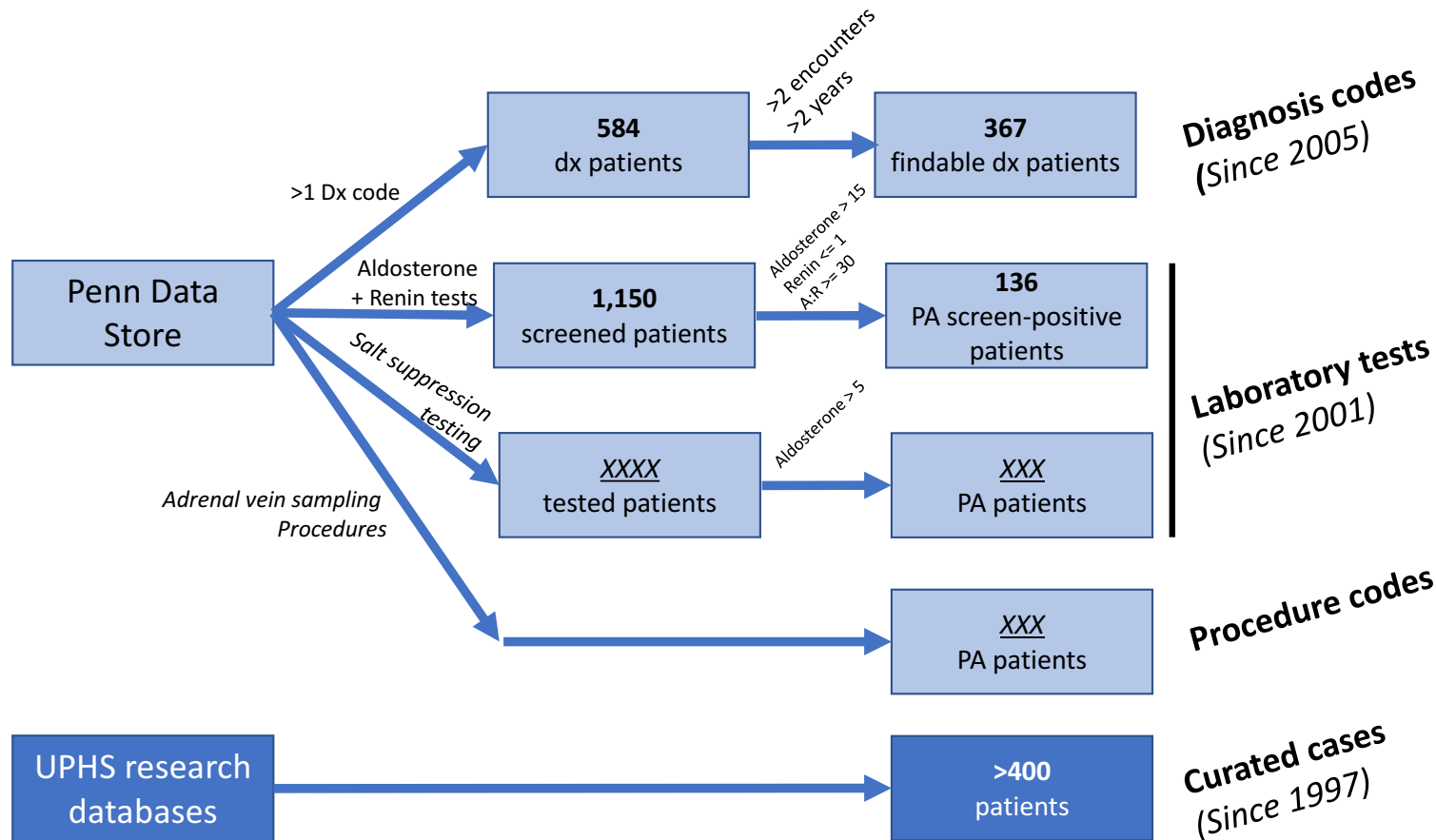


TABLE I. Characteristics of Patients With Primary Aldosteronism by AVS

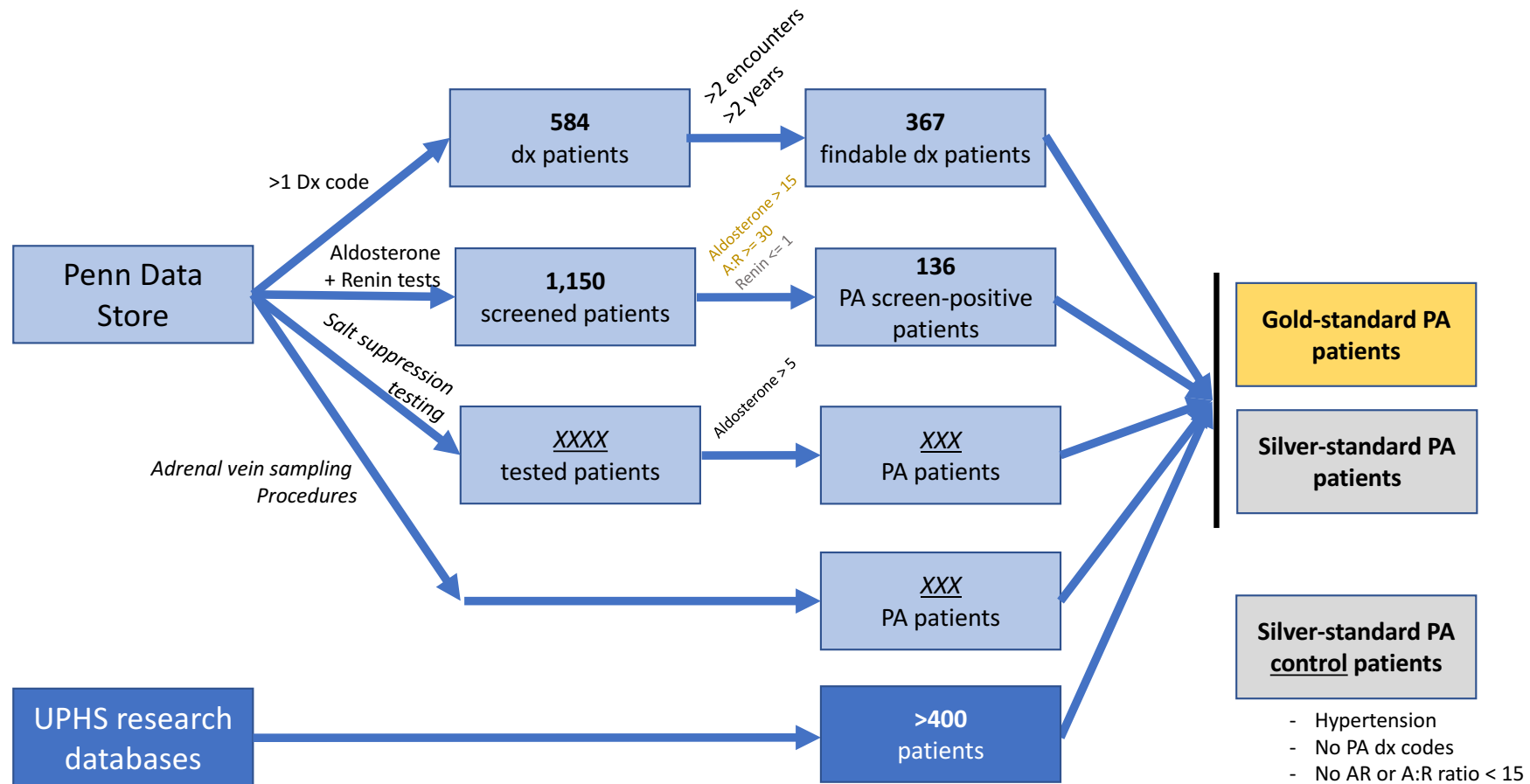
	AVS performed (n = 345)	No AVS performed (n = 22)
Age, years		
Mean (SD)	54 (11)	48 (11)
Gender		
Female (%)	133 (39)	10 (45)
Male (%)	212 (61)	12 (55)
BMI, kg/m <sup>2</sup>		
Median (IQR)	31 (27–36)	29 (25–34)
Ethnicity		
Caucasian (%)	186 (54)	10 (45)
African-American (%)	89 (26)	6 (27)
Asian (%)	12 (3)	0 (0)
Hispanic (%)	11 (3)	0 (0)
Other (%)	8 (2)	6 (27)
Missing (%)	39 (11)	0 (0)
Duration of hypertension, years		
Median (IQR)	10 (4–20)	6 (2–15)
Serum creatinine, mg/dl		
Median (IQR)	1.0 (0.8–1.2)	0.9 (0.8–1.0)
Plasma aldosterone concentration, ng/dl		
Median (IQR)	29 (19–42)	31 (16–62)
Plasma renin activity, ng/ml/hr		
Median (IQR)	0.3 (0.1–0.5)	0.1 (0.1–0.3)
Aldosterone-renin ratio, (ng/dl)/(ng/ml/hr)		
Mean (SD)	120 (60–230)	198 (63–277)
Imaging results		
Right sided mass (%)	91 (26)	5 (23)
Left sided mass (%)	156 (45)	13 (59)
Bilateral masses (%)	20 (6)	1 (5)
No masses (%)	78 (23)	3 (14)
Adrenalectomy (%)	199 (58)	18 (82)
Surgical pathology <sup>a</sup>		
Adenoma (%)	162 (81)	14 (78)
Dominant adenoma with hyperplasia (%)	28 (14)	4 (22)
Unilateral hyperplasia (%)	7 (4)	0 (0)
Other benign finding (%)	2 (1)	0 (0)
Median tumor size, cm (IQR) <sup>a</sup>	1.4 (1.0–2.0)	1.8 (1.4–2.7)

SD, standard deviation; IQR, interquartile range; AVS, adrenal vein sampling.  
<sup>a</sup>Surgical pathology and tumor size refer only to patients who underwent adrenalectomy.

Wachtel 2016

Resources: Penn Data Store, EPIC Clarity

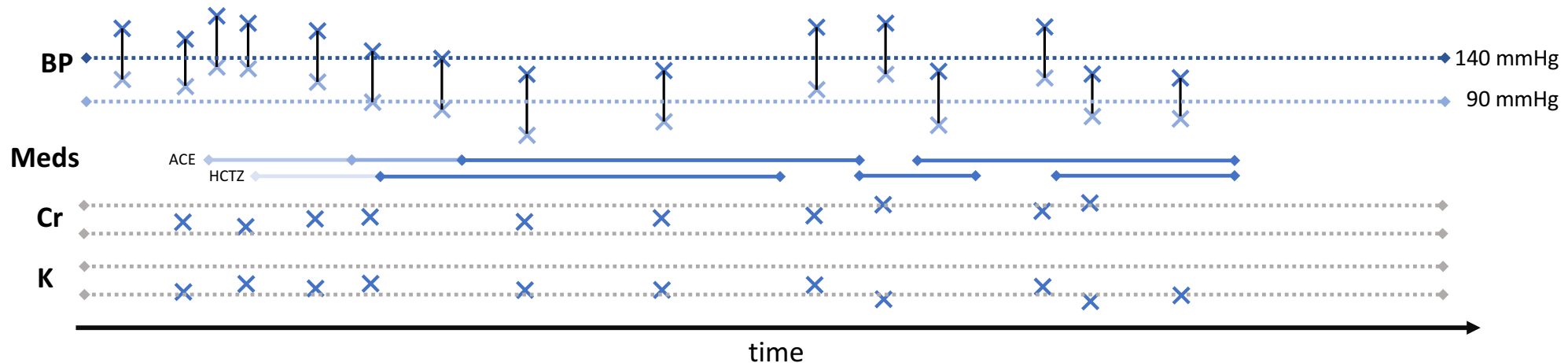
# Aim 1: Identify UPHS patients with known PA



Resources: Penn Data Store, EPIC Clarity

# Aim 1 – secondary goals

- Depict patient course and identify factors associated with PA



- PA diagnostic testing management

## CAP TODAY

### Primary aldosteronism: diagnostic team lifts clinical practice

William Check, PhD  
For decades, Michael Laposata, MD, PhD, chair of pathology at the University of Texas Medical Branch in Galveston, has touted the value of diagnostic management teams, and in February he led the first conference dedicated to such teams, referred to as DMTs. There, Allison Woodworth, PhD, told the story of how and why she created a DMT for primary hyperaldosteronism, what it achieved, and where her DMT focus is now.

### DMT-driven interpretation of high-risk hypertensive patient

**Comment:** This patient is a 53-year-old female with history of uncontrolled hypertension. At her visit she was hypokalemic with a potassium of 2.9 mEq/L (reference range: 3.3–4.8), and had normal renal function with a creatinine of 0.83 mg/dL (reference range: 0.57–1.11). The aldosterone/plasma renin activity ratio (ARR) is >102, with aldosterone of 20.4 ng/dL (reference range <35.3) and plasma renin activity of <0.2 ng/mL/hr (reference range: 0.7–3.3). At the time of specimen collection the patient was taking lisinopril and amlodipine which both decrease the ARR. Despite this, these results are **LIKELY** to represent primary aldosteronism. An endocrine consult is recommended. For further information on the effects of medications and comorbidities on the ARR, consider the additional information below:

[PA DMT Inference Table](#)

For additional information on specimen collection requirements please consult the following:

[PA DMT Specimen Collection Table](#)

### PA DMT details

■ Meets regularly

■ Relevant clinical history

■ Results considered in light of confounding factors

■ Evidence-based recommendations

**Table 3.** Factors That May Lead to False-Positive or False-Negative ARR Results

Factor	Effect on Aldosterone Plasma Levels	Effect on Renin Levels	Effect on ARR
<b>Medications*</b>			
β-Adrenergic blockers	D	D	U (FP)
Central agonists (eg, clonidine, α-methylglutamate)	D	D	U (FP)
NSAIDs	D	D	U (FP)
K <sup>+</sup> -wasting diuretics	R	U	D (FN)
K <sup>+</sup> -sparing diuretics	U	U	D (FN)
ACE inhibitors	D	U	D (FN)
ARBs	D	U	D (FN)
Ca <sup>2+</sup> blockers (DHPs)	R	U	D (FN)
Renin inhibitors	D	U	D (FN)
<b>Potassium status</b>			
Hypokalemia	D	R	D (FN)
Potassium loading	U	R	U
<b>Dietary sodium</b>			
Sodium restriction	U	U	U (FN)
Sodium loading	D	D	U (FP)
<b>Advancing age</b>	D	D	U (FP)
<b>Premenopausal women (vs males)*</b>	R	D	U (FP)
<b>Other conditions</b>			
Renal impairment	R	D	U (FP)
PHN-2	R	D	U (FP)
Pregnancy	U	U	D (FN)
Renovascular HT	U	U	D (FN)
Malignant HT	U	U	D (FN)

### B. Conditions for blood collection

1. Collect blood midmorning, after the patient has been up (sitting, standing, or walking) for at least 2 hours and seated for 5–15 minutes.
2. Collect blood carefully, avoiding stasis and hemolysis (see A.1 above).
3. Maintain sample at room temperature (and not on ice, as this will promote conversion of inactive to active renin) during delivery to laboratory and prior to centrifugation and rapid freezing of plasma component pending assay.

### C. Factors to take into account when interpreting results (see Table 3)

1. Age: in patients aged >65 years, renin can be lowered more than aldosterone by age alone, leading to raised ARR.
2. Gender: premenstrual, ovulating females have higher ARR levels than age-matched men, especially during the luteal phase of the menstrual cycle, during which false positives can occur, but only if renin is measured as DRC and not as PRA (220).
3. Time of day, recent diet, posture, and length of time in that posture
4. Medications
5. Method of blood collection, including any difficulty doing so
6. Level of potassium
7. Level of creatinine (renal failure can lead to false-positive ARR)

*2016 Endocrine PA Screening Guidelines*



# Aim 2: Algorithm to identify undiagnosed PA

## The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline

John W. Funder, Robert M. Carey, Franco Mantero, M. Hassan Murad,  
Martin Reincke, Hirotaka Shibata, Michael Stowasser, and William F. Young, Jr

Implement screening in patient groups enriched for PA:

	Resistant hypertension	Hypertension + hypokalemia	Hypertension + obstructive sleep apnea	Hypertension + Family Hx of HTN or stroke < 40 yo	Hypertension + 1 <sup>st</sup> degree relative with PA
	Hypertension	Resistant hypertension	Never on MR antagonist	No blood aldosterone or renin	
Encounters	189,068	5,724	4,742	4,324	
Patients	98,447	2,377 (2%)	2,068 (2%)	1,937 (2%)	

*UPHS outpatient  
encounters in 2015 and 2016*

# Aim 2 – Algorithm development

## Screening guidelines

Resistant hypertension

Hypertension + hypokalemia

Hypertension + obstructive sleep apnea

Hypertension + Family Hx of HTN or stroke < 40 yo

Hypertension + 1<sup>st</sup> degree relative with PA

## Evaluating electronic health record data sources and algorithmic approaches to identify hypertensive individuals

Pedro L Teixeira,<sup>1</sup> Wei-Qi Wei,<sup>1</sup> Robert M Cronin,<sup>1</sup> Huan Mo,<sup>1</sup> Jacob P VanHouten,<sup>1,2</sup> Robert J Carroll,<sup>1</sup> Eric LaRose,<sup>3</sup> Lisa A Bastarache,<sup>1</sup> S. Trent Rosenbloom,<sup>1,4</sup> Todd L Edwards,<sup>1</sup> Dan M Roden,<sup>4,5</sup> Thomas A Lasko,<sup>1</sup> Richard A Dart,<sup>6</sup> Anne M Nikolai,<sup>3</sup> Peggy L Peissig,<sup>3</sup> and Joshua C Denny<sup>1,4</sup>

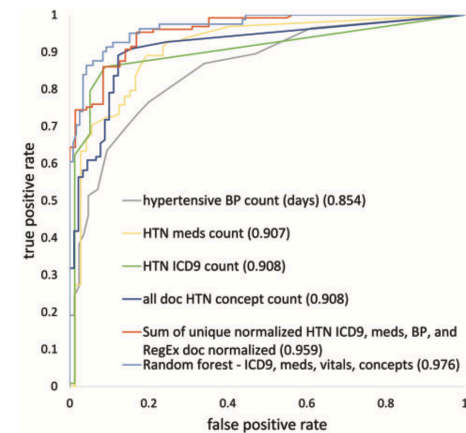
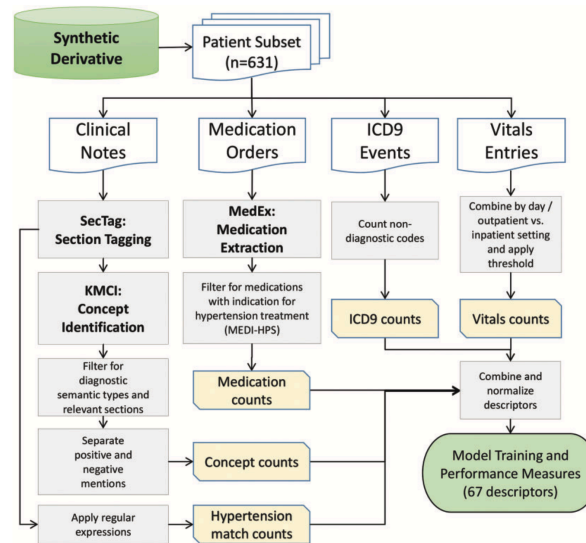
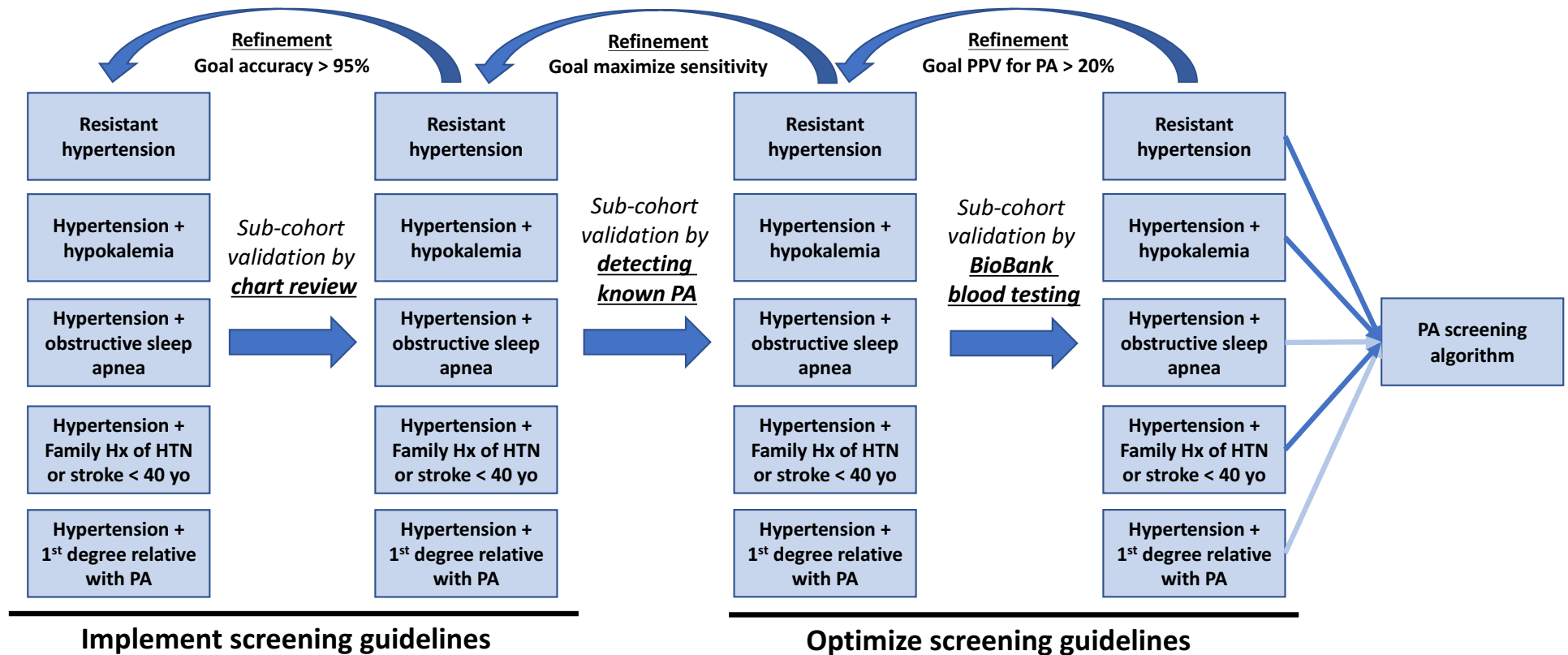


Table 2. Portability evaluation across various algorithms at Vanderbilt and Marshfield Clinic.

Model with expected features	Vanderbilt (n = 631)			Replication Marshfield (n = 100)		
	AUC (CI)	Sens.	PPV	AUC	Sens.	PPV
ICD9, meds, all BP (random forest)	0.955 (0.934–0.975)	0.844	0.954	0.922	0.966	0.919
ICD9, meds, all vitals (random forest)	0.961 (0.938–0.980)	0.858	0.954	0.910	0.966	0.905
ICD9, meds, all vitals, RegEx (random forest) <sup>a</sup>	0.967 (0.948–0.985)	0.866	0.954	0.934	0.966	0.934
ICD9, meds, all vitals, concept (random forest)	0.976 (0.95–0.984)	0.902	0.952	0.873	0.966	0.864
ICD9, meds, all vitals, RegEx, concepts (random forest) <sup>a</sup>	0.968 (0.951–0.985)	0.877	0.954	0.898	0.966	0.891
Positive category count ICD9, med, and BP 2 of 3	0.833 (0.788–0.868)	0.952	0.822	0.646	1.000	0.670
Positive category count ICD9, med, and BP 3 of 3	0.877 (0.849–0.914)	0.798	0.967	0.914	0.949	0.918
Positive category count ICD9, med, BP, and concept 3 of 4	0.910 (0.868–0.936)	0.925	0.924	0.711	0.983	0.716
Sum of normalized hypertension ICD9, meds, and BP	0.915 (0.888–0.942)	1.000	0.673	0.949	1.000	0.702
Sum of normalized hypertension ICD9, meds, BP, and concept	0.929 (0.897–0.955)	1.000	0.663	0.949	1.000	0.702

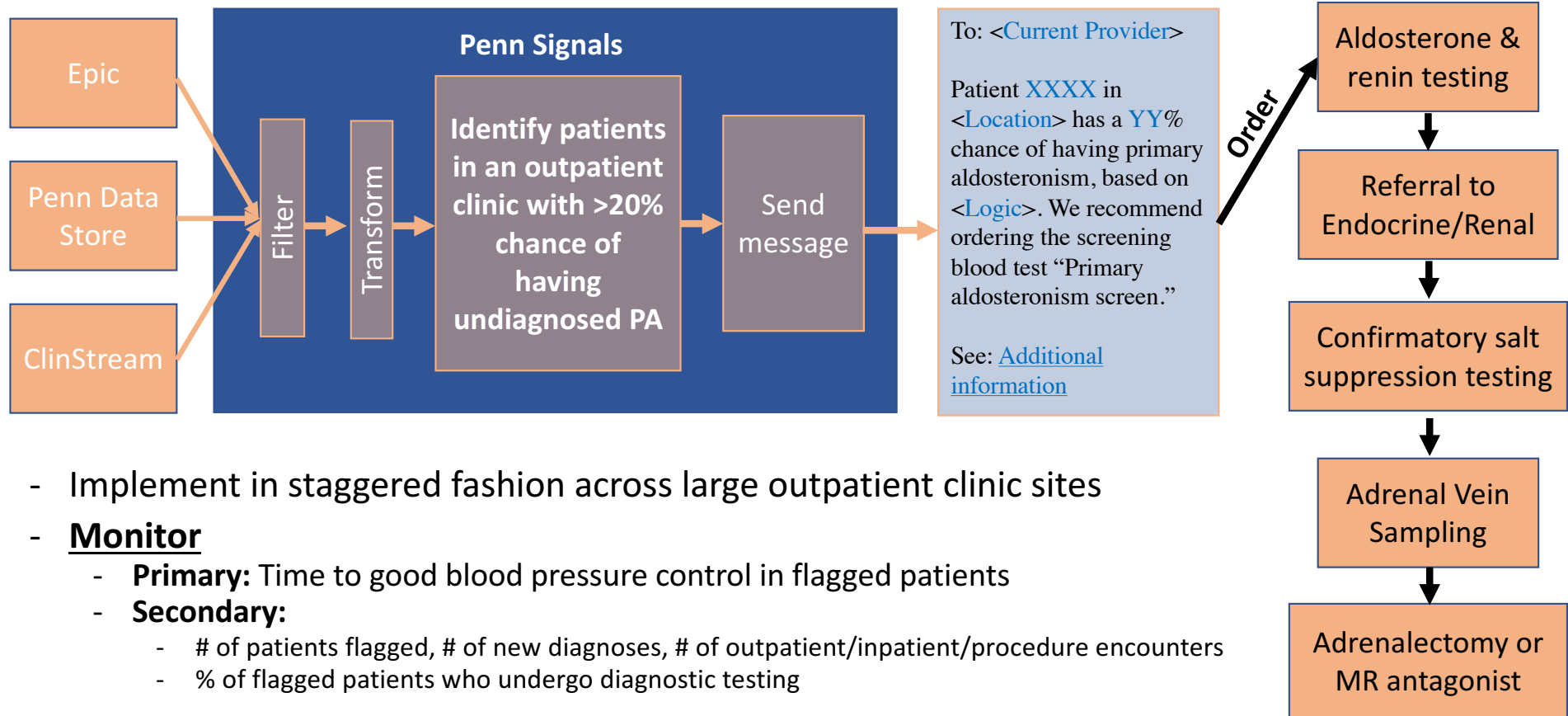
Resources: Penn Data Store, EPIC Clarity, IBI Clinical Informatics Core, ?Linguamatics, ?TURBO, Penn Signals

# Aim 2 – Algorithm development



Resources: DAC PDS/EPIC Clarity, SCRCM RedCap, PM BioBank, IBI Clinical Informatics Core, ?Linguamatics, ?TURBO, Penn Signals

## Aim 3 (Year 2): Implement CDS for diagnosis of PA



- Implement in staggered fashion across large outpatient clinic sites
- **Monitor**
  - **Primary:** Time to good blood pressure control in flagged patients
  - **Secondary:**
    - # of patients flagged, # of new diagnoses, # of outpatient/inpatient/procedure encounters
    - % of flagged patients who undergo diagnostic testing

Resources: PM Predictive Healthcare Penn Signals, DAC PDS/EPIC Clarity

Thank you!

