**Title**

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

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**Abstract**

Hypertension is the strongest, modifiable risk factor for cardiovascular disease. Primary aldosteronism (PA) comprises approximately 5% of hypertension. It is a treatable disorder, but is identified in fewer than 10% of affected patients. Moreover, in those patients, it is not found until after a median of 10 years of poorly controlled blood pressure. We propose to develop systematic, automated electronic health record (EHR)-based screening tools to improve the detection and management of PA. First, we will build algorithms using blood pressure, medication, laboratory, and diagnosis code data to identify UPHS patients who meet PA screening guidelines. By comparing and contrasting historical clinical data in these patients to that of patients with known PA or screened for PA, we will refine our algorithm to specifically identify patients with undiagnosed PA. To validate the resulting method and verify the burden of PA under-diagnosis, in a subset of flagged patients, we will use BioBank specimens to perform diagnostic blood aldosterone concentration and renin activity tests. Finally, we will implement the derived method as clinical decision support that recommends to primary care providers that they evaluate flagged patients for PA. The success of this approach will be assessed, as part of a staggered implementation phase, by comparing time to blood pressure control in flagged patients between trial and control sites.

1. **Mission and Specific Aims**

Preventing cardiovascular disease is a critical target for precision medicine, because it is the most common cause of morbidity and mortality.1,2 The strongest modifiable risk factor for cardiovascular disease is hypertension.3 We expend immense effort treating hypertension, and yet, only half of hypertensive patients are well-controlled.2 Hypertension is a multi-factorial disease and there is much variability in how individual patients respond to antihypertensive agents.4 However, in practice, we do not predict responses, but rather perform trial-and-error experiments for each patient.4

**Primary aldosteronism (PA) is responsible for hypertension in approximately 5% of affected patients**.5-7 PA is most commonly due to aldosterone-producing adenomas (APAs) or bilateral adrenal hyperplasia (BAH). In both cases, inappropriately high production of aldosterone leads to increased renal retention of sodium and water, along with increased renal excretion of potassium and H+.8 This dysregulation causes hypertension and cardiovascular injury. Compared to matched patients with essential hypertension, PA is associated with an increased incidence of stroke and myocardial infarction.9 However, when identified, APAs can be cured by adrenalectomy and BAH treated with mineralocorticoid receptor antagonists.10-12

Clinical guidelines8 recommend screening for PA in patients with sustained elevated blood pressure (SBP > 140, DBP > 90) that is resistant to three antihypertensive drugs13,14,15, hypertension with hypokalemia, hypertension with obstructive sleep apnea,16,17 hypertension with stroke at young age, and hypertension with a first-degree relative with PA. In patients for whom PA is suspected, we test the blood concentration of aldosterone and blood concentration or activity of renin. Elevated aldosterone and suppressed renin is specific for PA.7,18,19 However, in practice, it has more modest sensitivity and positive predictive value, because of patient factors that confound test interpretation, including medications, hypokalemia, and sodium intake.20,21 Most screen-positive patients undergo salt suppression testing to confirm the diagnosis, followed by cross-sectional imaging and adrenal vein sampling to distinguish between APA and BAH.

**Despite the burden of PA and the availability of specific treatments, PA is extremely underdiagnosed; it is not recognized in up to 99% of affected patients**.22 In UPHS since 2014, only 393 (0.2%) of the 189,068 patients prescribed anti-hypertensives appear to be diagnosed with PA, suggesting that ~10,000 UPHS PA patients may be undiagnosed. In addition, those patients identified were found after many years of poorly controlled hypertension. Among the 367 PA patients cared for at UPHS between 1997 and 2013, the median duration of hypertension prior to PA diagnosis was 10 years.23

**To meet this critical unmet need, we propose initiation of a new research program to develop systematic, automated solutions to enable earlier and more sensitive diagnosis of PA.** First, we will identify all UPHS patients with diagnosed PA. Next, we will develop an algorithm based on existing clinical guidelines to identify patients likely to have undiagnosed PA. Finally, we will implement this algorithm as clinical decision support. We expect this tool to increase the diagnosis of PA. This will benefit newly diagnosed patients by improving blood pressure control, and will translate into substantial reductions in risk for cerebrovascular events and myocardial infarction. To accomplish this goal we will:

**Aim 1: Identify and characterize UPHS patients with known primary aldosteronism.** We will combine data in existing research databases and Penn Data Store to identify all patients diagnosed with PA and explore their recorded clinical histories to find features that will enable the diagnosis of these patients earlier in their disease course and enable the identification of undiagnosed patients.

In preliminary studies of Penn Data Store, we identified 593 patients with at least two PA diagnostic codes (ICD10: E26.0\*, E26.9; ICD9 255.1, 255.10, 255.11, 255.12). Of these patients, 379 (64%) had at least 3 previous encounters spread over at least 2 years. This preliminary algorithm will be improved by querying for adrenal vein sampling procedures, aldosterone and renin laboratory results suggestive of PA, and cross-referencing retrospective research databases curated by Drs. Debbie Cohen, Scott Trerotola, and Douglas Fraker.23,24 We will refine criteria by iterative adjustment and focused chart review. Finally, the method’s positive predictive value will be assessed prospectively.

To find clinical features that may improve this method, we will characterize the retrospective PA cohort, focusing on plausible PA associations not previously reported. We will explore each patient’s hypertensive disease course and management by describing longitudinal blood pressures, antihypertensive therapy (medications, time intervals, doses), and laboratory results, as well as BP response to medications and comorbidities. We will also study patients not diagnosed with PA but tested for aldosterone and renin or treated with a mineralocorticoid antagonists. The comparison of these populations to PA patients will reveal variability in current practice and shed light on the importance of clinical factors known to interfere with the screening blood tests’ interpretations.

**Aim 2: Develop an algorithm to identify UPHS patients with undiagnosed primary aldosteronism.**

We will build *algorithms to identify patients who meet PA clinical screening guidelines* and validate results by chart review and blood testing of BioBank specimens, revealing current PA screening practices, estimating the potential for improving PA diagnosis, and creating an algorithm to detect undiagnosed PA.

First, we will build algorithms using Penn Data Store medications, blood pressures, diagnosis codes, and laboratory results to identify patients recommended for PA screening by the 2016 Endocrine Guidelines.8 Automating these guidelines will be challenging, because of the incompleteness of medication data, patient adherence, and clinical information not in structured data*.* We will ensure that this method finds all known PA patients with preceding UPHS encounters. Algorithms will be refined by focused chart review and iterative adjustment.

To estimate the minimal potential benefit of systematic screening, among known PA patients, we will calculate the diagnostic delay between screening algorithm, post-hoc positivity and PA diagnosis and translate time intervals into changes in expected morbidity, based on literature event rates. We will then trial the screening algorithm by selecting 100 BioBank blood specimens from flagged patients, with at least 3 years of UPHS encounters, for ARUP aldosterone and renin activity testing. The test positivity rate will enable estimation of the potential for increasing PA diagnosis and titration of the algorithm based on goal positive predictive value.

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|  | **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%) |

In preliminary analyses of Penn Data Store, since 2014 there have been 189,068 outpatient encounters for 98,447 patients with BP > 140/90 mmHg. Amongst these encounters, 2,377 patients were prescribed at least 50% max dose of the three anti-hypertensive drug classes. Of these, 1,937 patients have neither been prescribed a mineralocorticoid receptor antagonist since 2010 nor had a blood aldosterone or renin test since 2000. If 10% of these patients were ultimately diagnosed with PA, it would double our diagnosis rate.

Table 1: Primary aldosteronism screening criteria for UPHS outpatient encounters in 2016

As future work to improve these algorithms, we will apply natural language processing and ontologic frameworks (TURBO) to capture additional clinical information, including outside data and medication adherence. In addition, we will train machine learning algorithms on longitudinal structured EHR data to identify PA patients more specifically and earlier in their disease course.

**AIM 3 (Year 2): Prospectively implement clinical decision support to improve the diagnosis and management of primary aldosteronism.** We will implement the algorithms developed in AIM 2 as a clinical decision support tool and *trigger recommendations to primary care providers* that they evaluate individual patients for PA by screening laboratory testing. We expect to increase PA diagnoses and decrease time to blood pressure control in flagged patients.

To apply the developed algorithm clinically, we will first titrate it to make sure the positive predictive value is at least 20%. We will then build a clinical decision support rule within EPIC to alert patients’ primary care providers and recommend evaluation for primary aldosteronism by blood aldosterone and renin testing. Patients with positive or borderline results will be referred to specialists for additional workup. To enable estimation of the effect of this intervention, we will initially rollout this tool in a staged fashion amongst the six major UPHS outpatient sites, trialing initially in 1 site for 1 week, then 3 sites for 3 months, and then all sites.

The primary outcome measures followed will be the time between when a patient met PA screening criteria and both when they underwent PA laboratory screening and when their blood pressure was well-controlled. Secondary outcomes will include time from initial hypertension diagnosis to PA laboratory screening, increase in PA diagnosis rate, decrease in the prevalence of resistant hypertension, and change in the number of clinical encounters for hypertension.

1. **Clinical Impact**

Hypertension is sorely lacking precision medicine. The proposed project Aims 1 & 2 will build clinical informatics infrastructure and methods that will enable implementation of clinical decision support (Aim 3). These tools will **facilitate the diagnosis of hundreds of additional UPHS patients with PA, enabling us to offer targeted, effective medical or surgical therapy.** This targeted therapy will immediately benefit individual patients by improving their blood pressure control and thereby decreasing their risk of myocardial infarction, stroke, and other cardiovascular disease. In addition, we expect this project to yield net economic benefits by directly decreasing the number of outpatient visits to manage poorly controlled hypertension and by indirectly decreasing the burden of future cardiovascular disease.

The assembled interdisciplinary team will be critical for the design and implementation of the pre-clinical and clinical projects, because the project scope requires expertise from and interaction amongst primary care providers, specialists who care for PA patients, laboratorians responsible for the diagnostic laboratory testing, and practitioners specializing in clinical informatics and clinical decision support.

1. **Organization and Leadership**

This study will be led by Daniel Herman, MD, PhD. Dr. Herman is an Assistant Professor in the Department of Pathology, Division of Laboratory Medicine and is the medical director of the HUP Endocrinology Laboratory. Dr. Herman has a translational research program in predicting and preventing cardiovascular disease that includes clinical retrospective studies, laboratory operational quality improvement projects, and computational EHR analytics. He has extensive experience working with clinical data repositories and has generated the presented preliminary data. Julia Kharlip, MD is an Associate Professor of Medicine in the Division of Endocrinology who will apply her experience caring for PA patients to study design and interpretation. Jinbo Chen, PhD, an associate professor of Biostatistics and Epidemiology, will apply her experience in phenotype and effect heterogeneity to the design of the phenotyping algorithms. Daniel Rader, MD, Chair of the Department of Genetics and BioBank Medical Director, will provide guidance based on his experience in similar studies of familial hypercholesterolemia and BioBank expertise. Scott Damrauer, MD, Assistant Professor of Surgery, will provide guidance on study design based on his experience with clinical information systems and similar studies. David Birtwell, MSE, Director of Informatics for the BioBank and Technical Director of TURBO, will apply his extensive experience in converting Penn clinical data into knowledge. JoEllen Weaver, Technical Director of the Penn Medicine BioBank, will advise and coordinate the selection and testing of BioBank specimens. Craig Umscheid, MD, MSCE, Director of the Center for Evidence-based Practice and Medical Director of Clinical Decision Support, will advise on the design of study and implementation of clinical decision support.

1. **List of Penn Resources Utilized**

Penn Medicine BioBank, Data Analytics Core (Penn Data Store), Institute for Biomedical Informatics Transforming and Unifying Research with Biomedical Ontologies (TURBO) group, EPIC analyst team

1. **Metrics of Success**

* Development of an algorithm to accurately identify all patients with known PA
* Development of an algorithm to identify patients with undiagnosed PA with reasonable positive predictive value (>20%)
* Increase in the diagnosis rate of PA amongst UPHS patients by > 30%
* Decreased time to excellent blood pressure control in patients newly diagnosed with PA
* Decrease in the prevalence of resistant hypertension amongst UPHS patients

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