Modification

Basic Info

Confirmation Number:	**cdgbdjfg**
Protocol Number:	**827260**
Created By:	**HERMAN, DANIEL S**
Principal Investigator:	**HERMAN, DANIEL S**
Protocol Title:	**Development of tools to improve the detection of primary aldosteronism**
Short Title:	**Automated primary aldosteronism screening**
Protocol Description:	**We will build computational methods to screen for primary aldosteronism (PA) from existing clinical data. Algorithms will be validated by focused chart review and blood testing of specimens in the Penn Medicine BioBank. Finally, the validated method will be implemented prospectively to alert patients' providers of screen positive patients and recommend clinical evaluation for PA. We will monitor the impact of the recommendation on subsequent clinical care.**
Submission Type:	**Biomedical Research**

PennERA Protocol Status

Approved

Resubmission*
No

Are you submitting a Modification to this protocol?*

Yes

Current Status of Study

Study Status

Currently in Progress

If study is currently in progress, please enter the following

Number of subjects enrolled at Penn since the study was initiated

0

Actual enrollment at participating centers

0

If study is closed to further enrollment, please enter the following

Number of subjects in therapy or intervention

0

Number of subjects in long-term follow-up only

0

IRB Determination
If the change represents more than minimal risk to subjects, it must be reviewed and approved by the IRB at a convened meeting. For a modification to be considered more than minimal risk, the proposed change would increase the risk of discomfort or decrease benefit. The IRB must review and approve the proposed change at a convened meeting before the change can be implemented unless the change is necessary to eliminate an immediate hazard to the research participants. In the case of a change implemented to eliminate an immediate hazard to participants, the IRB will review the change to determine that it is consistent with ensuring the participant′s continued welfare. Examples: Convened Board Increase in target enrollment for investigator initiated research or potential Phase I research Expanding inclusion or removing exclusion criteria where the new population may be at increased risk Revised risk information with active participants Minor risk revisions that may affect a subject′s willingness to continue to participate Expedited Review Increase in target enrollment at Penn where overall enrollment target is not exceeded or potentially sponsored research Expanding inclusion or removing exclusion where the new population has the same expected risk as the previous, based on similarities of condition Revised risk information with subjects in long-term follow-up Minor risk revisions with no subjects enrolled to date
Expedited Review

Modification Summary
Please describe any required modification to the protocol. If you are using this form to submit an exception or report a deviation, enter 'N/A' in the box below.
Add study personnel

Risk / Benefit
Does this amendment alter the Risk/Benefit profile of the study?
No

Change in Consent
Has there been a change in the consent documents?
No

If YES, please choose from the options below regarding re-consenting

Deviations

Are you reporting a deviation to this protocol?*

No

Exceptions

Are you reporting an exception to this protocol?*

No

Protocol Details

Resubmission*
No

Study Personnel

Principal Investigator

Name:	**HERMAN, DANIEL S**
Dept / School / Div:	**4521 - PA-Pathology & Laboratory Medicine**
Campus Address Mail Code	**6082**
Address:	**PATH&LAB MED - M163 JM** **3620 HAMILTON WALK**
City State Zip:	**PHILADELPHIA PA 19104-6082**
Phone:	**267-226-3339**
Fax:	
Pager:	
Email:	**Daniel.Herman2@uphs.upenn.edu**
HS Training Completed:	**Yes**
Training Expiration Date:	**08/04/2017**
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**

Study Contacts

None

Other Investigator

None

Responsible Org (Department/School/Division):

4521 - PA-Pathology & Laboratory Medicine

Key Study Personnel

Name:	**WANG, LU**
Department/School/Division:	**SM-DN-Biomedical Graduate Studies**
HS Training Completed:	**Yes**
Training Expiration Date:	**04/29/2019**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**LYNCH, SELAH F**
Department/School/Division:	**BI-Institute for Biomedical Informatics**
HS Training Completed:	**Yes**
Training Expiration Date:	**05/12/2018**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**KHARLIP, JULIA N**
Department/School/Division:	**DM-Endocrinology, Diabetes & Metabolism**
HS Training Completed:	**Yes**
Training Expiration Date:	**09/06/2017**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**CHEN, JINBO**
Department/School/Division:	**BE-Biostatistics Division**
HS Training Completed:	**Yes**
Training Expiration Date:	**10/29/2018**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**ZHANG, LINGJIAO**
Department/School/Division:	**SM-DN-Biomedical Graduate Studies**
HS Training Completed:	**No**
Training Expiration Date:	
Name of course completed:	

Name:	**RIZER, NICHOLAS**
Department/School/Division:	**Health System**
HS Training Completed:	**Yes**
Training Expiration Date:	**04/03/2020**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**LO, YAN Y**
Department/School/Division:	**BI-Institute for Biomedical Informatics**
HS Training Completed:	**Yes**
Training Expiration Date:	**01/18/2019**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Disclosure of Significant Financial Interests*
Does any person who is responsible for the design, conduct, or reporting of this research protocol have a **FINANCIAL INTEREST**?
No

Certification
I have reviewed the *Financial Disclosure and Presumptively Prohibited Conflicts for Faculty Participating in Clinical Trials* and the *Financial Disclosure Policy for Research and Sponsored Projects* with all persons who are responsible for the design, conduct, or reporting of this research; and all required Disclosures have been attached to this application.
Yes

Biomedical Research

Investigator Initiated Trial
Is this an investigator-initiated trial?
Yes

Drugs or Devices*
Does this research study involve Drugs or Devices?
No

IND Exemption

For studies that fall under an IND exemption, please provide the number below

For studies including IND or IDE's, please provide the number(s) below

IDE Review*
NOTE: For research involving investigational devices, you are required to review the guidance on Managing Research Device Inventory. Consult the Penn Manual for Clinical Research: https://somapps.med.upenn.edu/pennmanual/secure/pm/investigational-product-management Please check the box Yes if you have reviewed the guidance.
No

Research Device Management*
Please indicate how research device(s) will be managed.
Not Applicable (no investigational devices)

Drug, Herbal Product or Other Chemical Element Management *
Please indicate how drugs, herbal products or other chemical entities will be managed.
Not Applicable (no drugs, herbal products or other chemical entities)

Radiation Exposure*
Are research subjects receiving any radiation exposure (e.g. X-rays, CT, Fluoroscopy, DEXA, pQCT, FDG, Tc-99m, etc.) that they would not receive if they were not enrolled in this protocol?
No

Gene Transfer*
Does this research involve gene transfer (including all vectors) to human subjects?
No

Human Source Material*
Does this research include collection or use of human source material (i.e., human blood, blood products, tissues or body fluids)?
Yes

CACTIS and CT Studies*
Does the research involve Center for Advanced Computed Tomography Imaging Services (CACTIS) and CT studies that research subjects would not receive if they were not part of this protocol?
No

CAMRIS and MRI Studies*
Does the research involve Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS) and MRI studies that research subjects would not receive if they were not part of this protocol?
No

Investigational Agent or Device within the Operating Room*
Does the research project involve the use of an investigational agent or device within the Operating Room?
No

Cancer Related research not being conducted by an NCI cooperative group*
Does this protocol involve cancer-related studies in any of the following categories?
No

Processing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)?
No

In-House Manufacturing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)?
No

Medical Information Disclosure*
Does the research proposal involve the use and disclosure of research subject's medical information for research purposes?
Yes

If the answer is YES, indicate which items is is provided with this submission:

Request for HIPAA Waiver of Authorization

CTRC Resources*
Does the research involve CTRC resources?
No

Pathology and Laboratory Medicine Resources*
Will samples be collected by hospital phlebotomy and/or processed or analyzed by any of the clinical laboratories of the University of Pennsylvania Health System?
No

Research Involves Apheresis, Cell Collection, and/or Blood Product Collection*
Does this research involve collection of blood products in the Penn Donor Center and/or the use of apheresis for treatment or collection of cells or other blood components?
No

Research involving blood transfusion or drug infusions*
Will your research involve blood transfusion or infusion of study drug in 3 Ravdin Apheresis Unit for research purposes?
No

Trial in Radiation Oncology
Is this research a prospective trial being done in Radiation Oncology, and if so, has this protocol been approved by the Radiation Oncology Protocol committee?
N/A

Study in Radiation Oncology
Is this research a retrospective study being done in Radiation Oncology, and if so, has this project been reviewed by the Radiation Oncology Clinical Research Group?
N/A

Use of UPHS services*
Does your study require the use of University of Pennsylvania Health System (UPHS) services, tests or procedures*, whether considered routine care or strictly for research purposes?
No

Primary Focus*
Research on human data sets (e.g. medical records, clinical registries, existing research data sets, medical administrative data, etc.)

Protocol Interventions

	Sociobehavioral (i.e. cognitive or behavioral therapy)
	Drug
	Device - therapeutic
x	**Device - diagnostic (assessing a device for sensitivity or specificity in disease diagnosis)**
	Surgical
	Diagnostic test/procedure (research-related diagnostic test or procedure)
	Obtaining human tissue for basic research or biospecimen bank
	Survey instrument
	None of the above

The following documents are currently attached to this item:

HIPAA Waiver of Authorization (irbrequestforwaiverofhipaaauthorization-forrelease_0-2.docx)

Department budget code

None

Multi-Site Research

Other Sites

No other sites

Management of Information for Multi-Center Research

The following documents are currently attached to this item:

There are no documents attached for this item.

Protocol

Abstract
The goal of our study is to enable earlier and more accurate diagnosis of primary aldosteronism (PA). PA is responsible for hypertension in ~1% of adults. Compared to matched patients with essential hypertension, PA is associated with an increased incidence of stroke and myocardial infarction. However, when identified, PA can be cured by adrenalectomy or treated with mineralocorticoid receptor antagonists. 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. In the initial phase of this project we will study retrospective EHR data and train models to identify patients with undiagnosed PA. In the final phase of the project, we will implement these methods prospective and provide clinical decision support to patients' providers recommending diagnostic testing.

Objectives

Overall objectives
- Develop automated methods to identify patients with undiagnosed primary aldosteronism - Build an application to implement the developed PA screening algorithms - Prospectively evaluate the developed tool as clinical decision support

Primary outcome variable(s)
Initial phase: positive predictive value of screening tools for identifying patients with primary aldosteronism Final phase: Number of patients diagnosed with primary aldosteronism, in clinical setting implementing clinical decision support and those not implementing clinical decision support

Secondary outcome variable(s)

- Frequency of diagnostic testing for primary aldosteronism (blood testing for renin and aldosterone) - The rate of false-positive PA diagnostic testing amongst screen-positive cases - Time to good blood pressure control in screen-positive patients

Background

PA is responsible for hypertension in ~1% of adults (1-3). Compared to matched patients with essential hypertension, PA is associated with an increased incidence of stroke and myocardial infarction (4). However, when identified, APAs can be cured by adrenalectomy and BAH treated with mineralocorticoid receptor antagonists (5-7). 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 (3,8,9). However, it has modest sensitivity and positive predictive value in clinical practice, because of patient factors that confound test interpretation, including medications, hypokalemia, and sodium intake (10,11). Therefore, only patients with suggestive signs are tested and screen-positive patients undergo confirmatory salt-suppression testing. 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 (12). Because of this underdiagnosis, the Endocrine Society recently published a Clinical Practice Guideline (13) recommending screening for PA in patients with sustained elevated blood pressure (SBP 140, DBP 90) that is resistant to three antihypertensive drugs(14-16), hypertension with hypokalemia, hypertension with obstructive sleep apnea (17,18), hypertension with stroke at young age, and hypertension with a first-degree relative with PA. We believe this study design is appropriate, because screening for PA meets a clear clinical need supported by society guidelines. These guidelines require systematic, automated methods for implementation. We believe it is appropriate to test this method as clinical decision support rather than a prospective clinical trial, because rather than prescribing clinical practice we are merely flagging particular patients and providing information for clinicians to use as part of their standard clinical practice. We do not think a full clinical trial is necessary, because of the strength of evidence behind the utility of making a PA diagnosis and because the clinician and patient will have the opportunity to decide how to use this information. 1. Douma S, Petidis K, Doumas M, Papaefthimiou P, Triantafyllou A, Kartali N, et al. Prevalence of primary hyperaldosteronism in resistant hypertension: a retrospective observational study. The Lancet. 2008 Jun;371(9628):19216. 2. Käyser SC, Dekkers T, Groenewoud HJ, van der Wilt GJ, Carel Bakx J, van der Wel MC, et al. Study Heterogeneity and Estimation of Prevalence of Primary Aldosteronism: A Systematic Review and Meta-Regression Analysis. The Journal of Clinical Endocrinology & Metabolism. 2016 Jul;101(7):282635. 3. Hannemann A, Wallaschofski H. Prevalence of Primary Aldosteronism in Patient's Cohorts and in Population-based Studies - A Review of the Current Literature. Horm Metab Res. © Georg Thieme Verlag KG; 2011 Dec 1;44(03):15762. 4. Milliez P, Girerd X, Plouin P-F, Blacher J, Safar ME, Mourad J-J. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. J. Am. Coll. Cardiol. 2005 Apr;45(8):12438. 5. Reincke M, Fischer E, Gerum S, Merkle K, Schulz S, Pallauf A, et al. Observational study mortality in treated primary aldosteronism: the German Conn's registry. Hypertension. American Heart Association, Inc; 2012 Sep;60(3):61824. 6. Lin Y-H, Lin L-Y, Chen A, Wu X-M, Lee J-K, Su T-C, et al. Adrenalectomy improves increased carotid intima-media thickness and arterial stiffness in patients with aldosterone producing adenoma. Atherosclerosis. 2012 Mar;221 (1):1549. 7. Catena C, Colussi G, Lapenna R, Nadalini E, Chiuch A, Gianfagna P, et al. Long-Term Cardiac Effects of Adrenalectomy or Mineralocorticoid Antagonists in Patients With Primary Aldosteronism. Hypertension. 2007 Oct 17;50(5):9118. 8. Montori VM, Young WF. Use of plasma aldosterone concentration-to-plasma renin activity ratio as a screening test for primary aldosteronism. A systematic review of the literature. Endocrinology and Metabolism Clinics of North America. 2002 Sep;31(3):61932xi. 9. Rossi GP, Bernini G, Caliumi C, Desideri G, Fabris B, Ferri C, et al. A Prospective Study of the Prevalence of Primary Aldosteronism in 1,125 Hypertensive Patients. J. Am. Coll. Cardiol. 2006 Dec;48(11):2293300. 10. Stowasser M, Ahmed A, Pimenta E, Taylor P, Gordon R. Factors Affecting the Aldosterone/Renin Ratio. Horm Metab Res. © Georg Thieme Verlag KG; 2011 Dec 6;44(03):1706. 11. Tomaschitz A, Pilz S. Aldosterone to Renin Ratio A Reliable Screening Tool for Primary Aldosteronism? Horm Metab Res. 2010 Mar 11;42(06):38291. 12. Funder J. Primary Aldosteronism: New Answers, New Questions. Horm Metab Res. © Georg Thieme Verlag KG; 2015 Dec 14;47(13):93540. 13. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism. 2016 May;101(5):1889916. 14. Calhoun DA, Nishizaka MK, Zaman MA, Thakkar RB, Weissmann P. Hyperaldosteronism Among Black and White Subjects With Resistant Hypertension. Hypertension.

2002;40(6):8926. 15. Gallay BJ, Ahmad S, Xu L, Toivola B. Screening for primary aldosteronism without discontinuing hypertensive medications: plasma aldosterone-renin ratio. American journal of . 2001;37(4):699705. 16. Eide IK, Torjesen PA, Drolsum A, Babovic A, Lilledahl NP. Low-renin status in therapy-resistant hypertension: a clue to efficient treatment. Journal of Hypertension. 2004 Nov;22 (11):221726. 17. Di Murro A, Petramala L, Cotesta D, Zinnamosca L, Crescenzi E, Marinelli C, et al. Renin-angiotensin-aldosterone system in patients with sleep apnoea: prevalence of primary aldosteronism. Journal of the Renin-Angiotensin-Aldosterone System. 2010 Sep 1;11(3):16572. 18. Dudenbostel T, Calhoun DA. Resistant hypertension, obstructive sleep apnoea and aldosterone. Journal of Human Hypertension. Nature Publishing Group; 2011 Jun 9;26(5):2817.

Study Design

Phase*
Not applicable

Design
This design does not cleanly fall within standard clinical trial phases. Initial study: Phase II, retrospective, longitudinal Final study: Phase III, prospective, clinical decision support, observational. Cross-over (implementation will be staggered across UPHS primary care groups)

Study duration
Initial study: Retrospective Final study: Begin 4/1/2018. 1 year of clinical decision support and 1.5 years of monitoring.

Resources necessary for human research protection
Describe research staff and justify that the staff are adequate in number and qualifications to conduct the research. Describe how you will ensure that all staff assisting with the research are adequately informed about the protocol and their research related duties. Please allow adequate time for the researchers to conduct and complete the research. Please confirm that there are adequate facilities for the research.
Human subject protection relates to subject confidentiality because there is no direct patient contact for this study. All study personal have received the appropriate CITI training and are experiences in the conduct of research with human subjects. Appropriate computer security measures are in place; all data that has PHI identifiers will be kept behind PHI firewall or on encrypted, password protected computers or digital media.

Characteristics of the Study Population

Target population
Adult subjects with undiagnosed primary aldosteronism

Subjects enrolled by Penn Researchers
100

Subjects enrolled by Collaborating Researchers
0

Accrual
Patients will be screened using automated tool, which will evaluate all UPHS patients by directly accessing clinical data. The sample size will be estimated based on results from first phase of study that will model current diagnosis rate and expected percent increase.

Key inclusion criteria
Age 18-110, any gender/sex.

Key exclusion criteria
Age less than 18.

Vulnerable Populations

	Children Form
	Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus) Form
	Fetuses and/or Neonates Form
	Prisoners Form
	Other
x	**None of the above populations are included in the research study**

The following documents are currently attached to this item:

There are no documents attached for this item.

Populations vulnerable to undue influence or coercion
N/A

Subject recruitment
Final stage: Automated decision support implemented via clinical health systems

Will the recruitment plan propose to use any Penn media services (communications, marketing, etc.) for outreach via social media avenues (examples include: Facebook, Twitter, blogging, texting, etc.) or does the study team plan to directly use social media to recruit for the research?
No

The following documents are currently attached to this item:

There are no documents attached for this item.

Subject compensation*
Will subjects be financially compensated for their participation?
No

The following documents are currently attached to this item:

There are no documents attached for this item.

If there is subject compensation, provide the schedule for compensation per study visit or session and total amount for entire participation, either as text or separate document

Study Procedures

Suicidal Ideation and Behavior
Does this research qualify as a clinical investigation that will utilize a test article (ie- drug or biological) which may carry a potential for central nervous system (CNS) effect(s)?
No

Procedures
For retrospective phase, Clinical data will be collected from CERNER Laboratory information system, laboratory middleware systems, and Penn Data Store by ODBC connections or related APIs. All locally stored data will be protected by remaining within UPHS network and by using physical protections (locked, restricted access rooms). Data will be verified and follow-up by focused chart review in Epic, Sunrise, and CERNER, as appropriate. For prospective phase, tool will directly query clinical data systems, perform calculations, and directly alert patients' providers via Epic Inbox.

The following documents are currently attached to this item:

There are no documents attached for this item.

Deception
Does your project use deception?
No

Analysis Plan
Data will be modeled using a variety of statistical and machine learning approaches to identify patterns and associations. Any findings will be validated in independent populations or the significance will be assessed by simulation and permutation.

The following documents are currently attached to this item:

There are no documents attached for this item.

Are you conducting research outside of the United States?
No

Data confidentiality

	Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.
x	**Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.**
x	**Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.**
x	**Wherever feasible, identifiers will be removed from study-related information.**
	A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.
	A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)
	Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.
	Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

Subject Confidentiality
All study personal have received the appropriate CITI training and are experienced in the conduct of research with human subjects and issues relating to subject confidentiality. Minimal datasets will be used with only PHI necessary for the conduct of the study. Chart review will only be performed by study personnel. All PHI extracted from health system will be stored digitally on computers within the UPHS firewall. The data will therefore be protected by UPHS credentials. No data will be stored on laptop computers. In addition, access will be restricted by file permissions to only study personnel. PHI will not be disclosed. If PHI will need to be stored on digital media or transferred outside of UPHS firewall, it will be encrypted and password protected. In the prospective phase of the study, patient's providers will be automatically alerted via Epic Inbox messages.

Sensitive Research Information*
Does this research involve collection of sensitive information about the subjects that should be excluded from the electronic medical record?
No

Subject Privacy
Privacy refers to the person's desire to control access of others to themselves. Privacy concerns people,

whereas confidentiality concerns data. Describe the strategies to protect privacy giving consideration to the following: The degree to which privacy can be expected in the proposed research and the safeguards that will be put into place to respect those boundaries. The methods used to identify and contact potential participants. The settings in which an individual will be interacting with an investigator. The privacy guidelines developed by relevant professions, professional associations and scholarly disciplines (e.g., psychiatry, genetic counseling, oral history, anthropology, psychology).
There is no active enrollment directly into this study and no direct subject contact.

Data Disclosure
Will the data be disclosed to anyone who is not listed under Personnel?
Yes. In the prospective phase, the tool will be used to make recommendations to clinical providers. This will include only UPHS clinical providers that the patient has already seen, either primary care provider, Endocrinologist, or Renal and Hypertension specialist. The data that will be revealed to this provider will not include any information that is not already in the patients EHR and already available to this clinician. Rather, it will include a synthesis of the patients existing EHR data.

*Data Protection**

x	**Name**
	Street address, city, county, precinct, zip code, and equivalent geocodes
x	**All elements of dates (except year) for dates directly related to an individual and all ages over 89**
	Telephone and fax number
	Electronic mail addresses
	Social security numbers
x	**Medical record numbers**
x	**Health plan ID numbers**
	Account numbers
	Certificate/license numbers
	Vehicle identifiers and serial numbers, including license plate numbers
	Device identifiers/serial numbers
	Web addresses (URLs)
	Internet IP addresses
	Biometric identifiers, incl. finger and voice prints
	Full face photographic images and any comparable images
	Any other unique identifying number, characteristic, or code
	None

Does your research request both a waiver of HIPAA authorization for collection of patient information and involve providing Protected Health Information ("PHI") that is classified as a "limited data set" (city/town/state/zip code, dates except year, ages less than 90 or aggregate report for over 90) to a recipient outside of the University of Pennsylvania covered entity?
No

Tissue Specimens Obtained as Part of Research*
Are Tissue Specimens being obtained for research?
No

Tissue Specimens - Collected during regular care*
Will tissue specimens be collected during regulator clinical care (for treatment or diagnosis)?
No

Tissue Specimens - otherwise discarded*
Would specimens otherwise be discarded?
No

Tissue Specimens - publicly available*
Will tissue specimens be publicly available?
No

Tissue Specimens - Collected as part of research protocol*
Will tissue specimens be collected as part of the research protocol?
No

Tissue Specimens - Banking of blood, tissue etc. for future use*
Does research involve banking of blood, tissue, etc. for future use?
No

Genetic testing
If genetic testing is involved, describe the nature of the tests, including if the testing is predicative or exploratory in nature. If predictive, please describe plan for disclosing results to subjects and provision of genetic counseling. Describe how subject confidentiality will be protected Note: If no genetic testing is to be obtained, write: "Not applicable."
Not applicable.

Consent

1. Consent Process

Overview
N/A

Children and Adolescents
N/A

Adult Subjects Not Competent to Give Consent
N/A

2. Waiver of Consent

Waiver or Alteration of Informed Consent*
Waiver or alteration of required elements of consent

Minimal Risk*
There are two potential risks to subjects: (1) If confidentiality is breached and PHI and associated clinical information is released. This risk is low because all study personnel have received appropriate CITI training and are experienced in the conduct of research with human subjects and issues related to subject confidentiality. Minimal datasets will be used with only PHI necessary for the conduct of the study. Chart review will only be performed by study personnel. All PHI extracted from health system will be stored digitally on computers within the UPHS firewall. The data will therefore be protected by UPHS credentials. No data will be stored on laptop computers. In addition, access will be restricted by file permissions to only study personnel. If PHI will need to be stored on digital media or transferred outside of UPHS firewall, it will be encrypted and password protected. (2) In the prospective study, some patients will be screen-positive, but do not have primary aldosteronism. Many patients will fall into this category. However, we feel this is appropriate and reasonable, because it is consistent with the current standard of care. In standard care, patients suspected of primary aldosteronism undergo screening. That screening is a blood test. If the blood test is positive, patients will undergo confirmatory testing; they will be given salt, either orally or intravenously, and then the same blood test will be repeated. This protocol will recommend additional patients for standard diagnostic screening; it will NOT replace the existing robust diagnostic testing. Thus, this proposed procedure will involve risk that

is equivalent to the current standard clinical care, and no more than minimal risk. To ensure this, we will monitor the rates of false-positive screen rates weekly and perform chart review of a subset monthly. In addition, the computational methods will be titrated such that the positive-diagnosis rate amongst screen-positive patients is consistent with the positive-diagnosis rate among current clinical screening practice (at least 10%). For patients with false-positive screens, the risk of subsequent invasive testing or change in medical management will be very low.

Impact on Subject Rights and Welfare*
This procedure will not mandate any clinical practice. All clinical decisions will be made as shared decisions between patient and his or her clinician. The waiver will not affect the patients options. In fact, the waiver is necessary to maximize the number of patients who will benefit from this procedure.

Waiver Essential to Research*
This waiver is absolutely necessary for the retrospective portion of this study, because the number of patients need for development of the computational method would be prohibitive. For the second phase of the research, it would not be practical to prospective enroll all patients for which the method is providing clinical decision support.

Additional Information to Subjects
In the prospective portion of study, information regarding the method and interpretation will be provided to the patients' provider, who will then have the opportunity to share that information with the patient.

Written Statement of Research*
No

If no written statement will be provided, please provide justificiation

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit

Potential Study Risks
There are two potential risks to subjects: (1) If confidentiality is breached and PHI and associated clinical information is released. This risk is low because all study personnel have received appropriate CITI training and are experienced in the conduct of research with human subjects and issues related to subject confidentiality. Minimal datasets will be used with only PHI necessary for the conduct of the study. Chart review will only be performed by study personnel. All PHI extracted from health system will be stored digitally on computers within the UPHS firewall. The data will therefore be protected by UPHS credentials. No data will be stored on laptop computers. In addition, access will be restricted by file permissions to only study personnel. If PHI will need to be stored on digital media or transferred outside of UPHS firewall, it will be encrypted and password protected. (2) In the prospective study, some patients will be screen-positive, but do not have primary aldosteronism. Many patients will fall into this category. However, we feel this is appropriate and reasonable, because it is consistent with the current standard of care. In standard care, patients suspected of primary aldosteronism undergo screening. That screening is a blood test. If the blood test is positive, patients will undergo confirmatory testing; they will be given salt, either orally or intravenously, and then the same blood test will be repeated. This protocol will recommend additional patients for standard diagnostic screening; it will NOT replace the existing robust diagnostic testing. Thus, this proposed procedure will involve risk that is equivalent to the current standard clinical care, and no more than minimal risk. To ensure this, we will monitor the rates of false-positive screen rates weekly and perform chart review of a subset monthly. In addition, the computational methods will be titrated such that the positive-diagnosis rate amongst screen-positive patients is consistent with the positive-diagnosis rate among current clinical screening practice (at least 10%). For patients with false-positive screens, the risk of subsequent invasive testing or change in medical management will be very low.

Potential Study Benefits
In the prospective phase of this study, the implemented tools will flag patients and recommend precision diagnostics. Subjects who are screened positive and diagnostic testing positive, will have the opportunity for curative surgery or precision medical management (depending on underlying type of primary aldosteronism). In addition, this method will be generally applicable to future patient populations outside of the study and serve to generally improve management of hypertension and decrease in subsequent cardiovascular disease.

Alternatives to Participation (optional)
Currently only 1-10% of patients with PA are diagnosed and those patients are diagnosed after a median of 10 years of poorly controlled hypertension. In the absence of this study, these patients are underserved. In addition, patients have the opportunity to take no action based on the study recommendations.

Data and Safety Monitoring
The Principal Investigator will be ultimately responsible for assuring the security of all data to minimize risk to participants.

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit Assessment
The benefit of early diagnosis and targeted treatment for patients with PA will outweigh the downside of additional blood testing in screen-positive PA-negative patients. To ensure this ratio is high enough, we will ensure that the rate of true-positive screens is at least 10%.

General Attachments

The following documents are currently attached to this item:

Cover Letter (cover_letter.docx)

Grant Application (herman.pcpmaf.proposal.final.pdf)

HIPAA Authorization or Waiver (irbrequestforwaiverofhipaaauthorization-forrelease_0-2.docx)