Genetic testing to Understand and Address Renal Disease Disparities (GUARDD)

Principal Investigator: Carol R. Horowitz, MD, MPH

ClinicalTrials.gov Identifier: NCT02234063

Protocol version: March 16, 2016

Genetic testing to Understand and Address Renal Disease Disparities (GUARDD)

Principal Investigator: Carol R. Horowitz, MD, MPH

ClinicalTrials.gov Identifier: NCT02234063

Protocol version: March 16, 2016

TABLE OF CONTENTS

1. BACKGROUND AND SIGNIFICANCE

1.1 Overview

Approaches and experiences of ongoing early adopter programs for incorporating genomic information in clinical care have to date been largely limited to examples conducted at a small group of academic institutions in few highly-specialized areas, including pharmacogenetics (1, 2), tumor-based screening (3, 4), family history-based decision support (5, 6), and diagnostic whole exome/genome sequencing (4, 7). However, studies that develop robust systems to consent, screen, return results, and that evaluate processes and outcomes of incorporating genomic risk information in clinical care for common chronic diseases are missing and urgently

needed. We propose that hypertension-attributable chronic kidney disease has emerged as a highly-relevant opportunity for a 'prototype' genomic medicine demonstration project that addresses common chronic illnesses managed in primary care settings. Hypertension-attributable chronic kidney disease (CKD) is characterized by

- high prevalence affecting millions of Americans (8),
- high burden of morbidity and mortality related mainly to increased cardiovascular disease risk and kidney failure or end stage renal disease (8),
- progression to kidney failure that can be modified by appropriate pharmacological interventions (9-11),
- a disproportionate burden for African Ancestry and major health disparity (12) (13-16) (17) (18),
- a substantial and testable population selective genomic risk that explains most of the excess burden of hypertension-attributable CKD risk in African Ancestry populations (19) (20) (21) (22).

Synthesis of evidence and formulation of study rationale

Synthesis: Chronic Kidney Disease (CKD), Hypertension and Blood Pressure Control. CKD is a common, complex disease affecting 26 million Americans adults (8). CKD is most commonly attributable to diabetes (40% of CKD cases) and hypertension (28% of cases). African Ancestry populations with hypertension (HTN) have 2- to 3-fold higher risk of developing CKD, and a 5-fold increased risk to progress to end stage renal disease (ESRD) when compared with whites. HTN is an established risk factor for progression of CKD and for increased cardiovascular risk with CKD. Thus targeting blood pressure control as a modifiable risk factor may both reduce CVD in people with CKD and reduce progression of CKD to end stage disease (9-11).

Synthesis: Poor adherence with renal care practice guidelines puts participants at risk for kidney failure

Importantly, major goals of practice guidelines for renal care in hypertensive participants remain unmet in clinical practice today: among Medicare participants with hypertension without diabetes, only 1 in 25 receives recommended simple lab tests (creatinine and urine albumin) to evaluate CKD, and less than half of all participants with moderate to advanced stages of CKD in the Kidney Early Evaluation Program (KEEP) are aware that they are affected (23). Among younger participants of African Ancestry CKD awareness is particularly low (23) and progression to kidney failure is typically accelerated resulting in excessive rates of ESRD (13) (18).

Improved CKD awareness and access to primary care or nephrology referral for individuals with or at risk of CKD are considered critical to improve CKD-related outcomes (24, 25). Factors associated with progression of CKD and with increased cardiovascular risk are overlapping to a large extent, including hypertension. There is strong evidence that blockade of the renin-angiotensin system is a blood pressure lowering strategy which is more effective in reducing risk of kidney and cardiovascular disease in the presence of albuminuria, a marker of CKD (26). Thus, in order to improved renal care and reduce risk for kidney failure in this population at excess risk, we urgently need new strategies:

- to improve comprehension of CKD risk and CKD awareness among participants with CKD or at risk for CKD and among their providers, and
- to increase adherence with practice guidelines targeting those risk factors that are modifiable may both reduce cardiovascular disease in people with CKD and reduce progression of CKD to end stage kidney disease.

Synthesis: *APOL1* G1 and G2 risk alleles and non-diabetic kidney diseases.

A locus containing the myosin heavy chain 9 (MYH9) gene for non-diabetic kidney disease in African ancestry individuals was initially identified by admixture mapping (27, 28). Recently, three non-synonymous coding

variants in the neighboring *APOL1* gene defined two allele, termed G1 and G2 with stronger effect on non-diabetic kidney disease than MYH9 variants (19). The authors suggested that G1 and G2 alleles are exceedingly rare in non-African ancestry genomes, but in African ancestry genomes, 22.5% and 14.6% of chromosomes carry the mutually-exclusive G1 and G2 risk alleles because they were selected for by providing protection against Trypanosomiasis (sleeping sickness) in West Africa (19).

APOL1-associated kidney disease risk is best explained using a recessive model, and approximately 13% of African Americans are estimated homozygous for G1 / G2 risk alleles, suggesting that more than 3 million AA are at markedly increased risk for non-diabetic CKD (20). In our IPM Biobank, 15% of more than 5,000 AA participants were found to carry [2] risk alleles, and the odds for hypertensive CKD in this cohort were 2.7. We recently analyzed the effect of APOL risk alleles on severity of hypertension-attributed kidney disease in the African American Study of Kidney Disease and Hypertension (AASK) cohort (Table 1). *APOL1* risk alleles are highly significantly associated with CKD attributed to essential hypertension in non-diabetic AASK participants, and the odds for advanced kidney disease (significant proteinuria or serum creatinine >3 mg/dl) were >4-fold in carriers of [2] risk alleles compared to [0,1] risk alleles (22). Heterozygous G1 or G2 risk allele status does not appear to increase kidney disease risk.

Table 1. Logistic regression model of the effect of APOL1 risk alleles on clinical phenotype AASK cases and controls

Note: creatinine >2 or >3 mg/dL approximate CKD Stage 3 or higher; ESKD indicates end stage kidney disease, i.e. CKD stage 5; urine PCR (protein creatinine ratio) > 0.22 g/g or > 0.60 g/g correlate approximately with albumin creatinine ratio (ACR) of > 30 mg/g and > 300 mg/g.

In summary, [2] *APOL1* G1 / G2 homozygous risk allele status

- explains practically all of the substantial excess genetic risk for non-diabetic CKD in African ancestry populations,
- is present in 1 out of 7 African American participants genotyped at Mount Sinai,
- is strongly and consistently associated with hypertension-attributable CKD (odds >2.7)
- is strongly and consistently associated with progressive and proteinuric states of hypertension-attributable CKD (odds >4.0) or with hypertensive ESRD (odds 7.3).

Thus, published evidence and our own Mount Sinai results strongly support our hypothesis that carriers of [2] *APOL1* risk alleles have an increased genomic risk for hypertension-attributable CKD and its progression to kidney failure.

1.2 Study Aims

GUARDD is multifaceted and has elements that involve qualitative research for a formative study to better information development of the randomized trial. This protocol is focused on the randomized controlled trial.

AIM II. Develop systems and evidence-based advice messages to enable point of care Clinical Decision Support (CDS) for primary care providers advising renal care practice guidelines with or without genomic *APOL1* risk information

Rationale. One of the highly anticipated quality improvement advantages offered by EHRs and 'meaningful use' is the potential for point of care Clinical Decision Support (CDS). CDS provides clinicians or participants with knowledge presented at appropriate times to improve healthcare. In this context, CDS also has the potential to increase the awareness of and adherence to, standard of care processes. Mount Sinai's IPM conducts several early adopter projects testing utility and adoption of pharmacogenomic CDS for clinicians in real-time at the point of care. We will develop new functionality for our existing CLIPMERGE Risk Assessment Engine database (CRAE database) to deliver CDS for renal care practice guidelines based on conventional kidney disease risk assessment with or without *APOL1* genomic kidney disease risk information. Importantly, we will for the first time develop interfaces that will allow CRAE to disseminate standardized CDS to independent Epic EHR implementations across different primary care practice settings at IFH and MSMC.

Sub-Aim 2.1. Modification of CLIPMERGE Risk Assessment Engine (CRAE) technology for multiple EHR (IFH and MSMC) and renal care CDS capabilities. CRAE houses phenotypic and gene variant data necessary for the evaluating enrolled participants' data relevant to the guidelines to be implemented for this study. The CRAE database will be populated only for enrolled participants. The CRAE database itself houses very strictly de-identified data (only). A separate function named the Broker handles all necessary translation between identified data (as needed for participant enrollment, for transactions flowing from and to Epic, and for receipt of genomic results from the CLIA lab) and de-identified data.

The **CLIPMERGE-EPIC Integration.** The CLIPMERGE database will include longitudinal clinical data extracted from Mount Sinai's and IFH's Epic EHR systems, for all consented participants enrolled in the research study; including CLIA-grade *APOL1* genotype and G1 G2 risk allele data from those that have been genotyped. Our CLIPMERGE Risk Assessment Engine (CRAE) includes this database and a rules engine that relates genome-based advice messages (renal care advice messages incorporating *APOL1* genomic risk information with conventional risk data) or conventional risk based advice messages to standard of care clinical decision support messages. During the first six months of year 1, the CLIPMERGE and Epic team at Mount Sinai will work with the Epic team at IFH to build HL7 interfaces customized between CRAE and the specific Epic version installed for IFH sites.

Reference and educational material. Upon presentation of a BPA, providers will have the opportunity to directly access reference content that further describes the evidence base for the CDS through a clickable link in the Epic SmartSet.

Sub-Aim 2.2. Development and usability testing of a library of evidence-based renal care advice messages customized for assessment of risk with and without *APOL1* G1 G2 risk allele information, and for adherence to practice guidelines for renal care in non-diabetic African ancestry participants with hypertension

Rationale. CKD awareness among participants and providers, appropriate use of tests for biochemical markers of CKD (creatinine and urinary albumin excretion) to screen for presence of CKD in those at risk, and appropriate use of pharmacological and life style interventions in those at risk for CKD progression are considered critical to improve CKD-related outcomes (ESRD, CVD, and mortality (24, 25). As summarized in the paragraph "**Synthesis: Poor adherence with renal care practice guidelines puts participants at risk for kidney failure"** at the beginning of the APPROACH section, major goals of practice guidelines for renal care in hypertensive participants remain unmet in clinical practice today. Blacks have higher prevalence of hypertension (41% vs. 28%), younger age of onset, and poorer control of hypertension than Whites (17). Blacks also have, a 2-3x the risk for developing CKD (12), and the adjusted prevalence rate for ESRD is 4.1-fold higher in AA when compared with Whites (14-16). The differences in CKD are most pronounced among those with hypertension. Thus, it is imperative to uncover new strategies to screen and engage AAs with hypertension into programs to improve BP control and participant outcomes.

The Kidney Disease Improvement Global Outcomes (KDIGO) evidence-based practice guidelines advise the appropriate use of tests for biochemical markers of CKD (creatinine and urinary albumin excretion) to screen for presence of CKD in those at risk, and appropriate use of pharmacological and lifestyle interventions in those at risk for CKD progression are considered critical to improve CKD-related outcomes (ESRD, CVD, and mortality (24, 25). Practice guidelines, including the Joint National Commission 7 (JNC7) guidelines, recommend specific medications (ACE inhibitors and ARBs) as preferred first line agents and more intensive blood pressure goal in participants with hypertensive CKD (9-11).

Several reports demonstrate that *APOL1* risk alleles are highly significantly associated with CKD attributed to essential hypertension in non-diabetic AASK participants, and the genetic association was most robust in individuals with progressive renal functional decline (22) (see our AASK Cohort data in Table 1). Because of the overwhelming strengths of the evidence, we propose to establish *APOL1* genomic risk status in non-diabetic AA participants and to incorporate the *APOL1* G1/G2 risk allele status in a recessive model together with conventional risk factors in CKD and CKD progression advice messages.

Aim III. Conduct a randomized trial assigning eligible participants to immediate genetic testing or delayed genetic testing arms in a seven (immediate testing) -to- one (delayed testing) ratio.

Sub-Aim 3.1: To examine whether increase in practice guideline-appropriate renal laboratory test ordering (renal care endpoint) will be achieved in *APOL1*-positive group vs *APOL1*-negative group.

Sub-Aim 3.2. To examine whether systolic blood pressure will decline more in the *APOL1*-positive group compared with *APOL1*-negative group.

2. ENDPOINTS

2.1 Primary Endpoints

The study has two primary endpoints, comparing patients who are *APOL1* positive (high risk) and *APOL1* negative at three months after enrollment. One primary aim is a renal care endpoint, the correct utilization, by clinicians, of urine albumin tests. The other primary aim is reduction of systolic blood pressure.

2.2 Secondary Endpoints

Secondary endpoints include differences between APOL1 positive participants in the intervention and participants in the control group, impact on primary outcomes at 12 months, psycho-behavioral differences of participants between groups and over time, clinician knowledge, attitudes and beliefs at baseline and 12 months, and differences in outcomes between those tested and not tested immediately.

3. STUDY DESIGN

3.1 Study Arms & Design

This is a prospective, multicenter, unblinded, randomized clinical trial (RCT) (**Figure 1**). The study was designed to randomize 2050 participants to immediate *APOL1* gene testing and return of results (ROR) (intervention) or delayed *APOL1* gene testing and ROR (control) in a 7:1 ratio. Outcome measures will be compared among three arms of the GUARDD study, the *APOL1*-positive and *APOL1*-negative intervention (immediate *APOL1* genetic testing and return of results) groups, and the control (delayed *APOL1* testing and return of results) group.

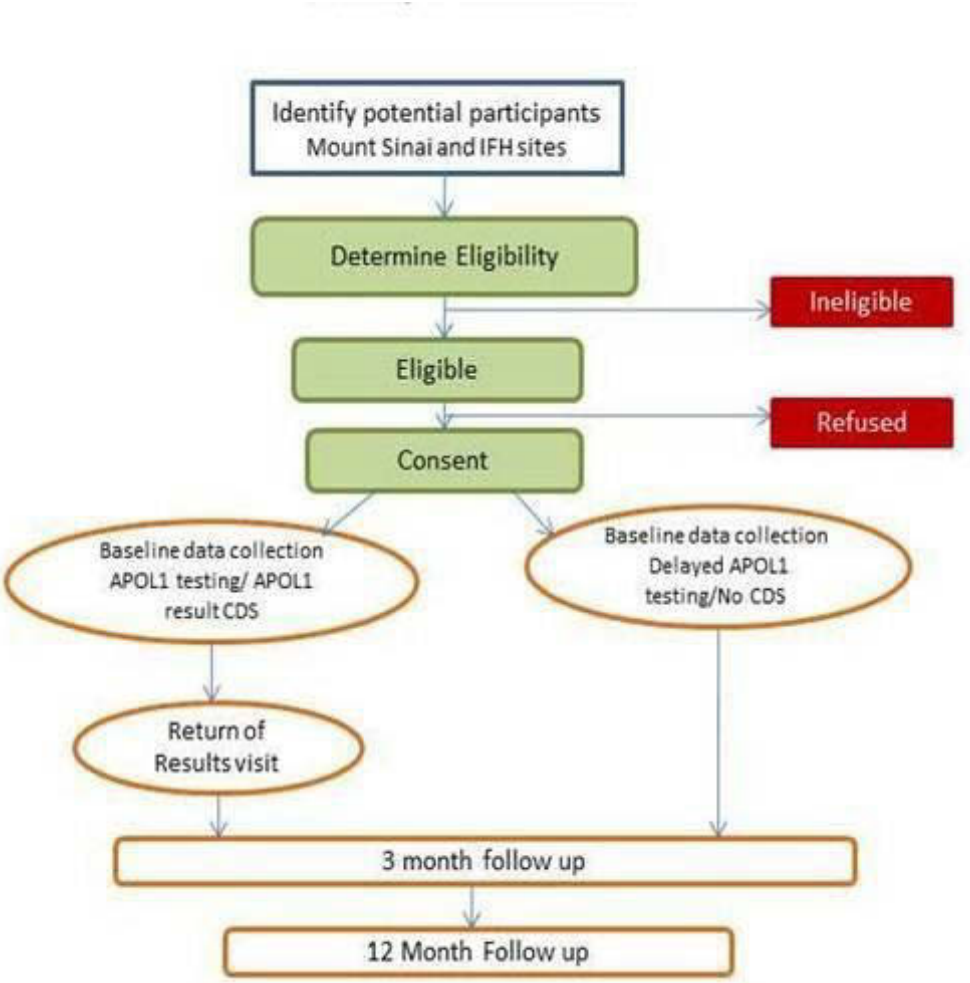


Figure 1. GUARDD study flowchart.

3.2 Randomization

Eligible participants will be randomized in a 7:1 allocation to Intervention (i.e., immediate *APOL1* gene testing and ROR to participant and provider) and Control arms (delayed *APOL1* gene testing and ROR to participant and provider) to optimize the proportion of participants with immediate *APOL1* genetic testing compared with delayed genetic testing at completion of study. Randomization will be stratified by clinical site with a random block size within site.

3.3 Blinding

GUARDD randomization assignments will not be blinded to any participants, providers or study personnel. To minimize bias in the measurement of the primary outcome, randomization assignments will only be revealed after baseline survey responses and blood pressure readings have been collected. Digital blood pressure devices (such as BpTru portable blood pressure machine (29)) will be used to measure blood pressure, and blood pressure will be measured as the mean of the second and third blood pressure readings for each participant at each study visit.

3.4 Sample Size

The total number of people expected to participate is 2,050. Of the 1800 intervention participants, approximately 250 will test positive. We will thus have approximately 250 high risk, 250 control, and 1550 normal risk participants. The sample size for the study was calculated assuming a 10% improvement in practice guideline-appropriate renal function test ordering in the *APOL1*-positive group (40% estimated) vs. *APOL1*-negative group (30% estimated) to yield 87% power to detect the difference of interest using a two-sided chi-square test. Specifically, this includes measurement of serum creatinine and urine microalbumin. The blood pressure sub-aim, 5mmHg improvement in systolic blood pressure at 3-month follow up in *APOL1*-positive compared with *APOL1*-negative group, can be detected with 95% power.

3.5 CCARP Genomics Subcommittee- Stakeholder Engagement

The CCARP Genomics Subcommittee members comprised of clinicians, researchers and community leaders will be in every stage of the research, including: choosing the study approach, tailoring and shaping the patient education materials, developing and implementing recruitment and retention strategies, deciding what to evaluate with survey questions, and disseminating our findings to the community.

4. STUDY POPULATION

4.1 Inclusion Criteria

- Self-reported African American/Black or having African Ancestry
- English speaking
- Age 18-70 years
- Have diagnosis of hypertension
    - Diagnosis of hypertension is defined by either:
        - ICD9 diagnosis codes (present in encounter diagnosis or in problem list) and/or
        - Taking anti-hypertensive medications or
        - 2 systolic blood pressure readings >140 mm Hg or 2 diastolic readings >90 at least six months apart.
- Received primary care from one of the participating clinical sites ≥1 within the past 2 years.
- Do not have diabetes by self report, or defined by:
    - ICD9 diagnosis codes (present in encounter diagnosis or in problem list) or
    - HbA1c ≥ 6.5 at least one time in the last year
- Do not have CKD by self report or defined by either:
    - 1) ICD9 codes OR
    - GFR < 60 ml/min

4.2 Exclusion Criteria

- Have diabetes measured or by self report
- Have CKD measured or by self report
- Pregnancy at time of enrollment by self report

- Too cognitively impaired to provide informed consent and/or complete the study protocol measured by mini mental status exam
- Institutionalized or too ill to participate (i.e. terminally ill, incarcerated, in psychiatric or nursing home facility) by self report
- Plan to move out of the area within 12 months of enrollment by self report
- Not a patient under the care of a provider for their hypertension at a participating site by self report
- Previously participated in the *APOL1* qualitative pilot study or have previously undergone *APOL1* testing

5. RECRUITMENT AND ENROLLMENT PROCEDURES

5.1 Participating Sites

Recruitment will be from primary care clinics within Mount and Institute for Family Health.

5.2 Provider Recruitment, Consent and Survey

We will present the study to providers at participating clinics and ask them to complete a short form consent explaining the purpose and the voluntary nature of their participation in the study. They will also receive the GUARDD APOL1 Provider Baseline Survey to be completed upon enrollment where we will ask questions about their current knowledge of genomics and personalized medicine and clinical decision support. At this time, we will also ask providers to give us permission to contact their patients who may be eligible to participate in the randomized trial and to have a recruitment letter sent to their patients signed by them or their practice. Providers who prefer to have a recruitment letter sent from them will provide a signature on a copy of the letter. As new providers join practices, we will also obtain their permission to contact their patients and ask them to complete the survey.

We will ask providers at participating sites to complete the GUARDD APOL1 12 Month Follow-Up Survey approximately 12 months after study enrollment. This questionnaire will contain similar questions asked at baseline, in addition to reactions to any clinical decision aids or exposure to APOL1 genetic testing over the course of the study. A list of participating providers will be kept by the study team to track completion of questionnaires and training attendance at the different study sites.

5.3 Participant Identification and Recruitment Strategies

<u>Participant Identification</u>

Electronic Health Record (EHR) Data Runs for Eligible Participants

Potential participants will be primarily identified through data runs using the inclusion criteria mentioned above. Lists with PHI identifying potential participants are emailed to the Program Manager via a secure, password protected Excel file. Participant's, date of birth, address and phone numbers, primary care provider name and clinic site extracted from the EHR are imported into the Redcap study database.

Referral

Participants may self-refer from any advertisement materials (posters, flyers). They may also be referred by a family member or friend, or by a provider who has agreed to allow their participants to participate in the study.

If a participant is referred, the Study Coordinator should check the REDcap database to ensure the participant is not already in the database and proceed accordingly.

Participant Recruitment

There are three main scenarios for recruitment:

- **Via recruitment letter:** Study Coordinators will be assigned participants (from the list of potentially eligible participants obtained through an Epic data run) and mail study recruitment letters to them. Letters are mailed in a bright blue envelope and postmarked with the GUARDD and clinic site logo to assist participants with recall and recognition. Participants can call us upon receiving the letter and they will then be screened for study eligibility. Study Coordinators will wait approximately 2 weeks after this mailing for a participant to return the letter refusing to participate, to call them, or to meet them at an upcoming clinic visit.
- **During a phone call:** If a participant does not return the refusal letter or contact us within 2 weeks of mailing, the Study Coordinator assigned to him/her will contact the participant by telephone. Using the recruitment phone script they will remind them about the letter that was mailed to them, introduce or reintroduce the study, screen them for eligibility, and answer any questions about the study.
- **During a clinic visit:** The Program Manager will receive a weekly list of which participants/potentially eligible participants have a scheduled clinic appointment and will notify the Study Coordinator assigned to that clinic site so s/he will plan to meet the participant at that time. The clinical Study Coordinator will discuss the study with the participant, screen them for eligibility, and answer any questions about the study.

Study Coordinators will then schedule all eligible and interested participants for a baseline visit. A baseline visit may occur at the time of recruitment (if approached at a clinic visit) or at a later date.

5.4 Screening Procedures

Study Coordinators will use a recruitment script during recruitment phone calls or clinic intercepts to inform the potential participant about the study and screen participants for eligibility using the study inclusion/exclusion criteria. If the participant is eligible and interested, a baseline visit will be scheduled that same day or for a future date.

5.5 Participant Consent Process

If a participant is interested and eligible, Study Coordinators will review the consent document at the start of the baseline study visit. Prospective research participants will have the opportunity to ask questions before providing written consent. Study Coordinators will provide the participant with a copy of the consent document. If the individual chooses not to sign the consent form, the Study Coordinator will inform him/her they are unable to participate in the study. The participant will also be provided the option to be contacted for future research.

5.6 Participant Discontinuation/Withdrawal from the Study

Participants may stop participating or withdraw from the study at any point in time. All information and data collected from the participant up to that point can be used in the study. Withdrawal of consent to participate in

the research study can be verbal or in writing. Study Coordinators should attempt to obtain a reason for withdrawal from the participant and record it in the study database.

Participants may withdraw from the study at any time by writing to the PI or by verbally informing the study coordinator or Program Manager. Any data collected up until withdrawal may be analyzed for study purposes but no new information will be collected.

5.7 Lost to Follow-Up

Losses to follow-up may be minimized and retention maximized through various mechanisms, including offering study visits during evening and weekend hours, collecting information for and contacting family members when participants cannot be reached, approaching research participants at clinic appointments, and completing surveys over-the-phone (although research participant should still attend study visits for blood pressure measurement). Certified letters may also be sent to those not reached by phone. Study Coordinators can confirm the best contact information for the participant at each study visit. Study Coordinators may also obtain permission to contact participants via text message or email and may send additional correspondence during the study. Participants may be assigned to a specific Study Coordinator at the site in order to maintain continuity and build rapport.

5.8 Risks

This research presents minimal risks to participants. Possible risks are described below.

<u>Blood Pressure</u>
Participants may feel some arm pressure when the blood pressure cuff is briefly inflated.

<u>Blood Draw</u>
The risks of a blood draw include pain, bruising, and the slight possibility of infection at the location of needle insertion. Some participants may feel dizzy or may faint during or after a blood draw.

<u>Saliva Collection</u>
Some people may feel discomfort because they cannot eat, drink, smoke or chew gum for 30 minutes before giving a saliva sample.

<u>Psychological Distress Learning of Test Results</u>
Results of the genetic test may show that a participant is at an increased risk of kidney disease. This knowledge may cause anxiety or psychological distress. Study staff will be trained to recognize anxiety and psychological stress and talk through this discomfort with the participant. All participants will have the option to speak with a genetic counselor if they choose.

5.9 Benefits

Participants may not receive any benefit from taking part in this research. Others may not benefit either. However, participants and their providers will obtain clinically-relevant genomic risk information to guide evaluation and treatment of hypertension and renal functioning, thus providing some indirect benefit to participant health.

5.10 Costs to the Participants

The costs of study-related genomic testing are covered by the study and will not be billed to participants. Taking part in this research study may lead to minor added costs including, for example, transportation to attend study visits. Participants (and/or their health care payer) will still be billed for the costs of their regular medical care that are not part of this study.

5.11 Compensation to Participants

Study participants will receive $40 in gift cards (to a variety of local retailers) at each of the Baseline, 3 Month and 12 Month follow-up visits. If a participant withdraws from the study before all visits are completed, they will be paid for any completed visits. If a participant is able to complete a survey over the phone for a follow up visit, but is unable to come in-person for a blood pressure measurement within the visit window, they will only receive a $20 gift card, which may be mailed to them at the address they provide.

6. STUDY PROCEDURES

6.1 Provider Surveys

Prior to first enrollment at a site, at one of their existing meetings, providers will be asked to complete a consent form to contact their potentially eligible participants and to complete the Baseline Provider Survey to assess demographics, knowledge, beliefs and practices around *APOL1* testing specifically and genetic testing more generally. This survey is anonymous. A GUARDD clinical champion will present the study to the providers of each site

6.2 Baseline Study Visit

Consent

The Study Coordinator will follow appropriate consenting protocol to consent interested and eligible participants.

Survey

After participants sign the informed consent, the Study Coordinators will confirm participant contact information and administer the GUARDD Baseline Survey using the REDCap database. Study Coordinators also have the option of administering surveys on paper and entering the responses in the RedCap database at a later date.

Biological Measures

Study Coordinators will obtain blood pressure using study specific protocols (outlined in the MOP) for blood pressure measurement using the BPTru portable blood pressure machine (29). If after several attempts, the study coordinator is unable to obtain an arm blood pressure measurement because the participant's arm is too large for the arm cuff or another reason, blood pressure will be measured using the Omron HEM 670IT wrist monitor and make a note in the participant's Redcap record. Study Coordinators will record the second and third blood pressure measurement in which will calculate the average blood pressure reading.

Study Coordinators will also measure participant height using the Charder HM200P portable stadiometer (at Baseline Visit only) and weight using the Detecto DR550C portable high capacity platform scale and input this information into the RedCap database which will calculate BMI.

Study Coordinators will record the average blood pressure and participant height and weight on the Personal Health Screening Form along with estimated dates for study follow up for the participant's personal records.

If the participant has a blood pressure reading greater than 190/110 during the study visit, study staff must complete an Elevated Blood Pressure Note for the participant, record the reading on REDCap, inform participant that they have very high blood pressure and strongly advise that they get urgent and appropriate evaluation and care from a healthcare provider. Study staff must also inform study PIs.

Specimen Collection

Participants will be randomized via the REDCap randomization tool using a stratified randomization scheme by clinical site in a 7:1 ratio of immediate or delayed *APOL1* genetic testing. The Study Coordinator informs the participant of their randomization outcome. A blood (preferred) or saliva sample is collected from participants randomized to immediate testing by the Study Coordinator. Study Coordinators will obtain a genetic sample for control participants at their 12 month visit. Participants are informed that their result will be ready in 2-4 weeks.

The baseline visit will take approximately 1.5 hours to complete. Participants will receive $40 in gift cards when they have completed their baseline visit.

6.3 Follow-Up Assessments

All participants will be advised that they will be contacted to complete a follow-up study visit at 3 months and 12 months after enrollment (duration of the observation period). During follow-up visits, Study Coordinators will follow study protocol (outlined in the MOP) to conduct surveys, measure blood pressure, and obtain participant weight in order to calculate body mass index. They will enter this data directly into REDCap using tablets/laptops. The follow-up visits will take approximately 45 minutes to complete. Participants will receive a $40 gift card for each follow-up visit completed.

Follow-up visits will be completed between 14 days prior and one month after the projected follow-up date (projected 3 month study visit due date = 3 months from date of baseline visit completion; projected 12 month study visit due date = 12 months from date of baseline visit completion). Whenever possible, participants will meet with the same Study Coordinator for follow-up visits to maintain continuity.

If the participant has a blood pressure reading greater than 190/110 during any follow up visit, study staff must complete an Elevated Blood Pressure Note, inform the participant that they have very high blood pressure and strongly advise that they get urgent and appropriate evaluation and care from a healthcare provider. Study staff must also inform study PIs.

6.4 Specimen Collection

Blood Specimen: At the baseline visit, Study Coordinators will consent participants if not previously consented, administer the baseline survey, take 3 blood pressure readings, measure participant height and weight and, if

trained in phlebotomy, collect 1 purple tops EDTA tube (approximately 3-5 mL) of venous blood from participants willing to provide a blood sample. If the Study Coordinator is not trained in phlebotomy, the participant will have their blood drawn by a trained phlebotomist. Participants will then be randomized to the Control or Intervention arm. Study Coordinators will label the tube with the participant ID, date of birth, sex and the date sample was collected, and follow the MOP for the collection, storage, and delivery of the sample to the laboratory.

Saliva Specimen: In the event that it is not possible to obtain a blood sample or participants prefer saliva collection, Study Coordinators will use an Oragene OG-500 kit to collect a saliva sample. They will label the sample and follow the saliva collection protocol for the collection, storage, and delivery of the sample to the laboratory as outlined in the MOP**.**

6.5 Specimen Transfer and Genetic Testing Procedures

Study Coordinators should store and directly transport specimens to the Mount Sinai Genetics Testing Laboratory, a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, according to procedures outlined in the MOP. Specimens will be accepted by the lab twice a week and processed on a weekly basis.

The *APOL1* G1/G2 genotype testing incorporates Polymerase Chain Reaction (PCR) and multiplex Allele Specific Primer Extension (ASPE) with Tm Bioscience's proprietary Universal Tag sorting system on the Luminex® 100 xMAP™ platform. Three SNP genotype in exon 6 are tested (RS73885319, RS60910145, RS71785313) to determine G1 and G1 allele status. To validate this genotyping method, at least three intra-assay and inter-assay runs involving 50 positive controls and 8 negative controls were performed. The positive control DNAs include samples which are heterozygous or homozygous for G1 and G2 genotypes. Negative controls are WT DNA for G1 and G2 alleles. Assays were 100% concordant reproducibly between the Luminex genotyping method and Sanger sequencing for each of the control samples.

6.6 Return of Genetic Results

Result reporting will occur approximately 1-4 weeks after the samples are obtained (see Fig. 1 Study flow chart). The laboratory will notify the study Program Manager of when results are ready to be returned. The Program Manager will in turn alert Study Coordinators. Return of results will be done by their assigned Study Coordinators. Study Coordinators will be trained by Randi Zinberg, Director of Mount Sinai Genetic Counseling Program, to return risk assessment results and recommendations. They will use a Return of Results Script for this visit. *APOL1* negative participants will have their tests results returned by phone (participants in the formative study said they did not want to come back in person for a negative results) and those that are *APOL1* positive will be scheduled for an in person return of results visit. If an in person return of results visit is not able to be scheduled for an *APOL1* positive participant, we will offer the participant the opportunity to receive their results over the phone. During return of results, the Study Coordinator will disclose the genetic test result, provide simple, clear information and use "speak back" or "teach back" technique to maximize participants' comprehension of their result. In addition to verbal ROR, participants will also receive lay explanations of their test results in writing and the educational booklet about *APOL1*, blood pressure and kidney

disease. *APOL1* positive participants will review the informational booklet at the time of their return of results, *APOL1* negative participants will receive their written test results and informational booklet in the mail.

If we are unable to return an *APOL1* positive test result to the participant for at least 3 months we will notify their primary care provider so that the result can be noted in their electronic health record and the participant can be notified of their results when they get in contact with their provider, even if that is after the study has ended.

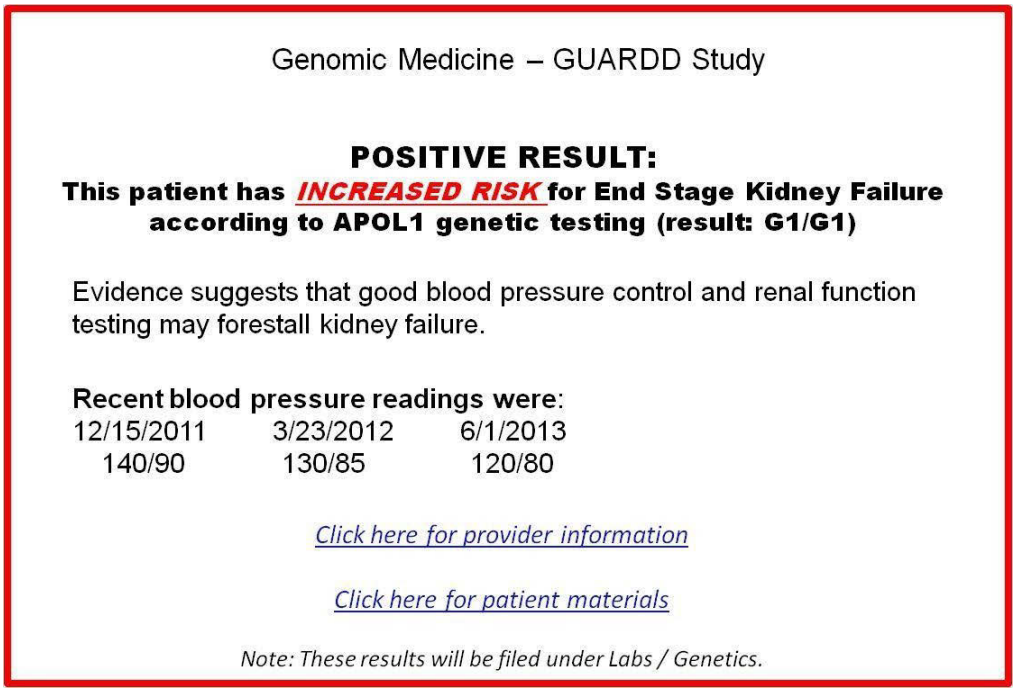
All participants will be given the option to speak to a genetic counselor after their return of results in person or by telephone, at no charge. If a participant chooses to speak with a genetic counselor, the Study Coordinator will contact the genetic counselor on behalf of the participant, and the genetic counselor will then follow-up directly with the participants.

Once a result is returned to the participant, the Study Coordinator completes the corresponding fields in Redcap that prompts CLIPMERGE to fire a Best Practice Alert (BPA) in the participant's electronic health record the next time a primary care provider opens it. The BPA will pop up once per unique provider. A provider can choose to open the BPA and has the option of clicking on and viewing and printing information for the participant and information for him/herself. In addition to the BPA, the lab will also place a copy of the *APOL1* genetic test results in the participant's electronic medical record. Electronic Health Record Data Extraction

6.7 Electronic Health Record Data Extraction

Electronic health data relevant to the study endpoints will be pulled for the period of 12 months prior to randomization and 12 months after randomization for all enrolled participants.

Figure 2. *APOL1* positive BPA Alert



6.8 Study Retention

Carefully trained, dedicated Study Coordinators that are from the same demographic groups and neighborhoods as participants will recruit participants, and will facilitate retention using relationship building, continuity with their assigned participants, sending personalized birthday and holiday cards, sending a 6 month check in postcard, placing a 9 month check in phone call, and collecting multiple contacts and modes of contact (e.g., phone, mail, text, email, intercepting at upcoming clinical appointments) from study participants. They will also "intercept" participants at clinical visits should they have clinical visits during the follow-up windows. If participants are unable to come to the practice for the entire visit, they can be surveyed by phone and come for blood pressure check, and if they cannot come at all, they can be surveyed by phone.

7. SAFETY ASSESSMENT AND MONITORING

The GUARDD Study is an observational-type study that does not include a drug or device intervention. For this reason, no adverse events will be collected or recorded in the study database. Adverse events suspected to be related to study interventions should be reported to the Mount Sinai and Institute for Family Health IRBs according to their local policies.

7.1 Distress from Return of Results

Distress from return of results will be monitored at participant visits. If the participant seems overly distressed by the outcomes of the genetic test results, the Research Coordinator will offer the participant the opportunity to speak to the genetic counselor. If the genetic counselor is not immediately available, the Research Coordinator will help coordinate a phone call or meeting with the genetic counselor based on participant's preference. The study coordinator will also inform the Project Manager and PI, document the event in the notes field of the participant's study database record, and follow-up with participant.

7.2 Elevated Blood Pressure Readings

If systolic blood pressure exceeds 190 mm Hg or diastolic exceeds 110 mm Hg during any study visit, the participant will be strongly advised to seek urgent and appropriate evaluation and care from a healthcare provider. The Research Coordinator may facilitate this by assisting the participant in contacting their primary care provider, urgent care, or clinic staff on site including the Principal Investigator (if study visit is taking place in a clinical setting) and by completing the Elevated Blood Pressure Note that participants may share with their provider.

8. STATISTICAL ANALYSIS PLAN AND SAMPLE SIZE

8.1 Sample Size Determination

The study will randomize 2050 patients to either immediate or delayed genetic testing in a ratio of 7:1 respectively. We anticipate that of the 1800 patients who will be tested immediately approximately 250 will test positive. For this aim, we hypothesize that APOL1 positive patients will achieve 40% correct utilization of serum creatinine and/or urine albumin tests for "standard renal care" in patients with hypertension, compared to

30% for APOL1 negative patients. With an estimated 250 APOL1 positive and 1550 APOL1 negative we will have 87% power to detect the difference of interest using a two sided chi-square test.

Power calculations for this sub-aim are based on reduction of systolic blood pressure at three months after enrollment. For patients who test APOL1 positive we anticipate a 5 mmHg reduction in systolic blood pressure, compared to no change in patients who test APOL1 negative. Assuming that the standard deviation for differences in blood pressure between baseline and 3 month in both arms is 20 mmHg, a total of 250 patients testing positive and 1550 testing negative provides approximately 95% power to detect a difference of 5 mmHg in SBP between these two groups. If the standard deviation is larger than assumed, say 25 mmHg, power will still exceed 80%. Power is based on a 0.05 level two-tailed t-test of the difference in SBP at 3 months.

8.2 General Statistical Methods

We will use mean and standard deviation to describe continuous variables, proportions for categorical variables; t-tests or analysis of variance (ANOVA) to compare continuous variables, and chi-square or Fisher's exact test to compare categorical variables by groups. To test significance of changes within groups over time, we will use paired t-tests for continuous and McNemar's tests for categorical variables. We will use linear mixed models to test the difference in SBP change over time between *APOL1* positives and negatives by entering the interaction term of time and *APOL1* status and adjusting for confounders, and generalized estimating equation methodology to test the change in controlled SBP status and renal function testing overtime between *APOL1* positives and negatives, and similarly between *APOL1* positives and controls.

8.3 Population for Analyses

Patients will be from academic, community and safety-net practices in New York City. Inclusion criteria are: self-identified AA; age 18–70 years; hypertension EHR diagnosis and/or taking antihypertensive medications, and/or 2 SBP readings >140mmHg at least six months apart; community-dwelling; English speaking; and receiving primary care at participating site in the past year. Exclusion criteria are: diabetes; CKD; pregnancy; moving away during the study period; and cognitive impairment.

8.4 Analysis of the Secondary Endpoints

Secondary outcomes include differences in SBP and urine testing in an enriched intervention group (*APOL1* positives) vs. controls, and psycho-behavioral patient factors between groups and over time.

8.5 Handling of Missing Data

Missing data will be analyzed as intention to treat.

9. DATA MANAGEMENT

9.1 Data Entry and Record Keeping

Data will be entered and stored in a REDCap database to track and monitor participants. The database was adapted from the data dictionary to include MRNs and participant IDs, inclusion criteria, baseline, 3- and 12-month participant contact logs and surveys, calendar and reminder functions, and ability for recruiters,

managers and investigators to track workflow and perform queries to assess the status of participants (i.e., who is outstanding for a 3-month ROR1 visit).

9.2 Database Management and Quality Control of Data

A REDCap database will be developed to track and monitor participants. This includes MRNs and participant IDs, inclusion criteria, baseline, 3- and 12-month participant contact logs and surveys, calendar and reminder functions, and ability for recruiters, managers and investigators to track workflow and perform queries to assess the status of participants (i.e., who is outstanding for a 3-month visit). Data will be entered into REDCap using tablets/laptops. Study staff will be trained on how to enter data and will receive a unique user identification and password to access data entry forms for their site. Access codes should not be shared and are non-transferable. Study Coordinators will always have paper survey copies as backup should Redcap be down or they experience technical difficulties.

Genetic test results are uploaded directly into the REDCap database through a CLIPEMERGE interface and verified by the Program Manager. The database includes password protection and internal quality checks, such as automatic range limits and regular checks to identify data that appear inconsistent, incomplete, or inaccurate. The Program Manager and study biostatistician will review the data on a regular basis as part of quality control. The check will review the data for errors, outliers, missing fields, inconsistencies, etc.

10. ETHICAL AND HUMAN SUBJECTS CONSIDERATIONS

10.1 Institutional Review Board

This study will be initiated only after all required documentation has been reviewed and approved by the Mount Sinai and Institute for Family Health Institutional Review Boards (IRBs).

10.2 Large Scale Data Sharing

The sharing of our dataset will follow the requirements set forth by the NIH policy for data sharing and guidelines for NIH Data Set Preparation. The de-identified and anonymized phenotype and genotype data will may be made available in NIH's database of Genotypes and Phenotypes (dbGaP) repository for sharing to the larger scientific community.

Databases, like dbGAP, were created to meet the needs of the medical genetics community by storing medical information from many studies conducted at many different places. Researchers can then study the combined information to learn even more about health and many different diseases. Some databases are publicly accessible and some are restricted. Anyone on the Internet can access the information shared in publicly accessible databases. However, only researchers who apply to restricted databases and are approved can access databases, like dbGAP. The current study will limit sharing of data to only those databases, which are restricted and require approval to access, like dbGAP that maintain Certificates of Confidentiality.

11. PROTOCOL DEVIATIONS

A protocol deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the protocol. Protocol deviations will be reported to the GUARDD Program Manager, Principal Investigator and Mount Sinai and Institutes for Family Health IRB according to their policies.

REFERENCES

1. Pulley, J.M., Denny, J.C., Peterson, J.F., Bernard, G.R., Vnencak-Jones, C.L., Ramirez, A.H., Delaney, J.T., Bowton, E., Brothers, K., Johnson, K., et al. 2012. Operational Implementation of Prospective Genotyping for Personalized Medicine: The Design of the Vanderbilt PREDICT Project. *Clinical pharmacology and therapeutics* 92:87-95.
2. Crews, K.R., Cross, S.J., McCormick, J.N., Baker, D.K., Molinelli, A.R., Mullins, R., Relling, M.V., and Hoffman, J.M. 2011. Development and implementation of a pharmacist-managed clinical pharmacogenetics service. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists* 68:143-150.
3. Gudgeon, J.M., Williams, J.L., Burt, R.W., Samowitz, W.S., Snow, G.L., and Williams, M.S. 2011. Lynch syndrome screening implementation: business analysis by a healthcare system. *The American journal of managed care* 17:e288-300.
4. Worthey, E.A., Mayer, A.N., Syverson, G.D., Helbling, D., Bonacci, B.B., Decker, B., Serpe, J.M., Dasu, T., Tschannen, M.R., Veith, R.L., et al. 2011. Making a definitive diagnosis: successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease. *Genetics in medicine : official journal of the American College of Medical Genetics* 13:255-262.
5. Khoury, M.J., Feero, W.G., and Valdez, R. 2010. Family history and personal genomics as tools for improving health in an era of evidence- based medicine. *American journal of preventive medicine* 39:184-188.
6. Orlando, L.A., Hauser, E.R., Christianson, C., Powell, K.P., Buchanan, A.H., Chesnut, B., Agbaje, A.B., Henrich, V.C., and Ginsburg, G. 2011. Protocol for implementation of family health history collection and decision support into primary care using a computerized family health history system. *BMC health services research* 11:264.
7. Bainbridge, M.N., Wiszniewski, W., Murdock, D.R., Friedman, J., Gonzaga-Jauregui, C., Newsham, I., Reid, J.G., Fink, J.K., Morgan, M.B., Gingras, M.C., et al. 2011. Whole-genome sequencing for optimized participant management. *Science translational medicine* 3:87re83.
8. Coresh, J., Selvin, E., Stevens, L.A., Manzi, J., Kusek, J.W., Eggers, P., Van Lente, F., and Levey, A.S. 2007. Prevalence of chronic kidney disease in the United States. *JAMA* 298:2038-2047.
9. Chobanian, A.V., Bakris, G.L., Black, H.R., Cushman, W.C., Green, L.A., Izzo, J.L., Jr., Jones, D.W., Materson, B.J., Oparil, S., Wright, J.T., Jr., et al. 2003. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 42:1206-1252.
10. Kidney Disease Outcomes Quality Initiative (K/DOQI). 2004. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis.* 43:S1-290.
11. Padwal, R.S., Hemmelgarn, B.R., Khan, N.A., Grover, S., McKay, D.W., Wilson, T., Penner, B., Burgess, E., McAlister, F.A., Bolli, P., et al. 2009. The 2009 Canadian Hypertension Education Program recommendations for the management of hypertension: Part 1--blood pressure measurement, diagnosis and assessment of risk. *The Canadian journal of cardiology* 25:279-286.
12. Muntner, P., Newsome, B., Kramer, H., Peralta, C.A., Kim, Y., Jacobs, D.R., Jr., Kiefe, C.I., and Lewis, C.E. 2012. Racial differences in the incidence of chronic kidney disease. *Clinical journal of the American Society of Nephrology : CJASN* 7:101-107.

13. Centers for Disease Control and Prevention (CDC). 2007. Racial differences in trends of end-stage renal disease, by primary diagnosis--United States, 1994-2004. *MMWR Morb Mortal Wkly Rep*. 56:253-256.
14. Hsu, C.Y., Lin, F., Vittinghoff, E., and Shlipak, M.G. 2003. Racial differences in the progression from chronic renal insufficiency to end-stage renal disease in the United States. *J Am Soc Nephrol* 14:2902-2907.
15. Tomson, C.R., Foley, R.N., Li, Q., Gilbertson, D.T., Xue, J.L., and Collins, A.J. 2008. Race and end-stage renal disease in the United States Medicare population: the disparity persists. *Nephrology (Carlton)* 13:651-656.
16. Freedman, B.I., Langefeld, C.D., Rich, S.S., Valis, C.J., Sale, M.M., Williams, A.H., Brown, W.M., Beck, S.R., Hicks, P.J., and Bowden, D.W. 2004. A genome scan for ESRD in black families enriched for nondiabetic nephropathy. *J Am Soc Nephrol* 15:2719-2727.
17. Hertz, R.P., Unger, A.N., Cornell, J.A., and Saunders, E. 2005. Racial disparities in hypertension prevalence, awareness, and management. *Archives of internal medicine* 165:2098-2104.
18. Tarver-Carr, M.E., Powe, N.R., Eberhardt, M.S., LaVeist, T.A., Kington, R.S., Coresh, J., and Brancati, F.L. 2002. Excess risk of chronic kidney disease among African-American versus white subjects in the United States: a population-based study of potential explanatory factors. *J Am Soc Nephrol* 13:2363-2370.
19. Genovese, G., Friedman, D.J., Ross, M.D., Lecordier, L., Uzureau, P., Freedman, B.I., Bowden, D.W., Langefeld, C.D., Oleksyk, T.K., Uscinski Knob, A.L., et al. 2010. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 329:841-845.
20. Friedman, D.J., Kozlitina, J., Genovese, G., Jog, P., and Pollak, M.R. 2011. Population-based risk assessment of APOL1 on renal disease. *Journal of the American Society of Nephrology : JASN* 22:2098-2105.
21. Birchenall-Roberts, M.C., Ruscetti, F.W., Kasper, J., Lee, H.D., Friedman, R., Geiser, A., Sporn, M.B., Roberts, A.B., and Kim, S.J. 1990. Transcriptional regulation of the transforming growth factor beta 1 promoter by v-src gene products is mediated through the AP- 1 complex. *Mol.Cell Biol.* 10:4978-4983.
22. Lipkowitz, M.S., Freedman, B.I., Langefeld, C.D., Comeau, M.E., Bowden, D.W., Kao, W.H.L., Astor, B.C., Bottinger, E.P., Iyengar, S.K., Klotman, P.E., et al. 2012. Apolipoprotein L1 gene variants associate with hypertension-attributed nephropathy and the rate of kidney function decline in African Americans. *Kidney international* In Press.
23. Agrawal, V., Jaar, B.G., Frisby, X.Y., Chen, S.C., Qiu, Y., Li, S., Whaley-Connell, A.T., McCullough, P.A., and Bomback, A.S. 2012. Access to health care among adults evaluated for CKD: findings from the Kidney Early Evaluation Program (KEEP). *American journal of kidney diseases: the official journal of the National Kidney Foundation* 59:S5-15.
24. Saab, G., Whaley-Connell, A.T., McCullough, P.A., and Bakris, G.L. 2008. CKD awareness in the United States: the Kidney Early Evaluation Program (KEEP). *American journal of kidney diseases: the official journal of the National Kidney Foundation* 52:382-383.
25. Plantinga, L.C., Boulware, L.E., Coresh, J., Stevens, L.A., Miller, E.R., 3rd, Saran, R., Messer, K.L., Levey, A.S., and Powe, N.R. 2008. Participant awareness of chronic kidney disease: trends and predictors. *Archives of internal medicine* 168:2268-2275.

26. Appel, L.J., Wright, J.T., Jr., Greene, T., Agodoa, L.Y., Astor, B.C., Bakris, G.L., Cleveland, W.H., Charleston, J., Contreras, G., Faulkner, M.L., et al. 2010. Intensive blood-pressure control in hypertensive chronic kidney disease. *The New England journal of medicine* 363:918-929.
27. Kao, W.H., Klag, M.J., Meoni, L.A., Reich, D., Berthier-Schaad, Y., Li, M., Coresh, J., Patterson, N., Tandon, A., Powe, N.R., et al. 2008. MYH9 is associated with nondiabetic end-stage renal disease in African Americans. *Nat Genet* 40:1185-1192.
28. Kopp, J.B., Smith, M.W., Nelson, G.W., Johnson, R.C., Freedman, B.I., Bowden, D.W., Oleksyk, T., McKenzie, L.M., Kajiyama, H., Ahuja, T.S., et al. 2008. MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. *Nat Genet* 40:1175-1184.
29. Wright, J. M., Mattu, G. S., Perry, T. L., Jr, Gelferc, M. E., Strange, K. D., Zorn, A., & Chen, Y. 2001. Validation of a new algorithm for the BPM-100 electronic oscillometric office blood pressure monitor. *Blood pressure monitoring*, *6*(3), 161–165. https://doi.org/10.1097/00126097-200106000-00008

needed. We propose that hypertension-attributable chronic kidney disease has emerged as a highly-relevant opportunity for a 'prototype' genomic medicine demonstration project that addresses common chronic illnesses managed in primary care settings. Hypertension-attributable chronic kidney disease (CKD) is characterized by

- high prevalence affecting millions of Americans (8),
- high burden of morbidity and mortality related mainly to increased cardiovascular disease risk and kidney failure or end stage renal disease (8),
- progression to kidney failure that can be modified by appropriate pharmacological interventions (9-11),
- a disproportionate burden for African Ancestry and major health disparity (12) (13-16) (17) (18),
- a substantial and testable population selective genomic risk that explains most of the excess burden of hypertension-attributable CKD risk in African Ancestry populations (19) (20) (21) (22).

Synthesis of evidence and formulation of study rationale

Synthesis: Chronic Kidney Disease (CKD), Hypertension and Blood Pressure Control. CKD is a common, complex disease affecting 26 million Americans adults (8). CKD is most commonly attributable to diabetes (40% of CKD cases) and hypertension (28% of cases). African Ancestry populations with hypertension (HTN) have 2- to 3-fold higher risk of developing CKD, and a 5-fold increased risk to progress to end stage renal disease (ESRD) when compared with whites. HTN is an established risk factor for progression of CKD and for increased cardiovascular risk with CKD. Thus targeting blood pressure control as a modifiable risk factor may both reduce CVD in people with CKD and reduce progression of CKD to end stage disease (9-11).

Synthesis: Poor adherence with renal care practice guidelines puts participants at risk for kidney failure

Importantly, major goals of practice guidelines for renal care in hypertensive participants remain unmet in clinical practice today: among Medicare participants with hypertension without diabetes, only 1 in 25 receives recommended simple lab tests (creatinine and urine albumin) to evaluate CKD, and less than half of all participants with moderate to advanced stages of CKD in the Kidney Early Evaluation Program (KEEP) are aware that they are affected (23). Among younger participants of African Ancestry CKD awareness is particularly low (23) and progression to kidney failure is typically accelerated resulting in excessive rates of ESRD (13) (18).

Improved CKD awareness and access to primary care or nephrology referral for individuals with or at risk of CKD are considered critical to improve CKD-related outcomes (24, 25). Factors associated with progression of CKD and with increased cardiovascular risk are overlapping to a large extent, including hypertension. There is strong evidence that blockade of the renin-angiotensin system is a blood pressure lowering strategy which is more effective in reducing risk of kidney and cardiovascular disease in the presence of albuminuria, a marker of CKD (26). Thus, in order to improved renal care and reduce risk for kidney failure in this population at excess risk, we urgently need new strategies:

- to improve comprehension of CKD risk and CKD awareness among participants with CKD or at risk for CKD and among their providers, and
- to increase adherence with practice guidelines targeting those risk factors that are modifiable may both reduce cardiovascular disease in people with CKD and reduce progression of CKD to end stage kidney disease.

Synthesis: *APOL1* G1 and G2 risk alleles and non-diabetic kidney diseases.

A locus containing the myosin heavy chain 9 (MYH9) gene for non-diabetic kidney disease in African ancestry individuals was initially identified by admixture mapping (27, 28). Recently, three non-synonymous coding

variants in the neighboring *APOL1* gene defined two allele, termed G1 and G2 with stronger effect on non-diabetic kidney disease than MYH9 variants (19). The authors suggested that G1 and G2 alleles are exceedingly rare in non-African ancestry genomes, but in African ancestry genomes, 22.5% and 14.6% of chromosomes carry the mutually-exclusive G1 and G2 risk alleles because they were selected for by providing protection against Trypanosomiasis (sleeping sickness) in West Africa (19).

APOL1-associated kidney disease risk is best explained using a recessive model, and approximately 13% of African Americans are estimated homozygous for G1 / G2 risk alleles, suggesting that more than 3 million AA are at markedly increased risk for non-diabetic CKD (20). In our IPM Biobank, 15% of more than 5,000 AA participants were found to carry [2] risk alleles, and the odds for hypertensive CKD in this cohort were 2.7. We recently analyzed the effect of APOL risk alleles on severity of hypertension-attributed kidney disease in the African American Study of Kidney Disease and Hypertension (AASK) cohort (Table 1). *APOL1* risk alleles are highly significantly associated with CKD attributed to essential hypertension in non-diabetic AASK participants, and the odds for advanced kidney disease (significant proteinuria or serum creatinine >3 mg/dl) were >4-fold in carriers of [2] risk alleles compared to [0,1] risk alleles (22). Heterozygous G1 or G2 risk allele status does not appear to increase kidney disease risk.

Table 1. Logistic regression model of the effect of APOL1 risk alleles on clinical phenotype AASK cases and controls

Note: creatinine >2 or >3 mg/dL approximate CKD Stage 3 or higher; ESKD indicates end stage kidney disease, i.e. CKD stage 5; urine PCR (protein creatinine ratio) > 0.22 g/g or > 0.60 g/g correlate approximately with albumin creatinine ratio (ACR) of > 30 mg/g and > 300 mg/g.

In summary, [2] *APOL1* G1 / G2 homozygous risk allele status

- explains practically all of the substantial excess genetic risk for non-diabetic CKD in African ancestry populations,
- is present in 1 out of 7 African American participants genotyped at Mount Sinai,
- is strongly and consistently associated with hypertension-attributable CKD (odds >2.7)
- is strongly and consistently associated with progressive and proteinuric states of hypertension-attributable CKD (odds >4.0) or with hypertensive ESRD (odds 7.3).

Thus, published evidence and our own Mount Sinai results strongly support our hypothesis that carriers of [2] *APOL1* risk alleles have an increased genomic risk for hypertension-attributable CKD and its progression to kidney failure.

1.2 Study Aims

GUARDD is multifaceted and has elements that involve qualitative research for a formative study to better information development of the randomized trial. This protocol is focused on the randomized controlled trial.

AIM II. Develop systems and evidence-based advice messages to enable point of care Clinical Decision Support (CDS) for primary care providers advising renal care practice guidelines with or without genomic *APOL1* risk information

Rationale. One of the highly anticipated quality improvement advantages offered by EHRs and 'meaningful use' is the potential for point of care Clinical Decision Support (CDS). CDS provides clinicians or participants with knowledge presented at appropriate times to improve healthcare. In this context, CDS also has the potential to increase the awareness of and adherence to, standard of care processes. Mount Sinai's IPM conducts several early adopter projects testing utility and adoption of pharmacogenomic CDS for clinicians in real-time at the point of care. We will develop new functionality for our existing CLIPMERGE Risk Assessment Engine database (CRAE database) to deliver CDS for renal care practice guidelines based on conventional kidney disease risk assessment with or without *APOL1* genomic kidney disease risk information. Importantly, we will for the first time develop interfaces that will allow CRAE to disseminate standardized CDS to independent Epic EHR implementations across different primary care practice settings at IFH and MSMC.

Sub-Aim 2.1. Modification of CLIPMERGE Risk Assessment Engine (CRAE) technology for multiple EHR (IFH and MSMC) and renal care CDS capabilities. CRAE houses phenotypic and gene variant data necessary for the evaluating enrolled participants' data relevant to the guidelines to be implemented for this study. The CRAE database will be populated only for enrolled participants. The CRAE database itself houses very strictly de-identified data (only). A separate function named the Broker handles all necessary translation between identified data (as needed for participant enrollment, for transactions flowing from and to Epic, and for receipt of genomic results from the CLIA lab) and de-identified data.

The **CLIPMERGE-EPIC Integration.** The CLIPMERGE database will include longitudinal clinical data extracted from Mount Sinai's and IFH's Epic EHR systems, for all consented participants enrolled in the research study; including CLIA-grade *APOL1* genotype and G1 G2 risk allele data from those that have been genotyped. Our CLIPMERGE Risk Assessment Engine (CRAE) includes this database and a rules engine that relates genome-based advice messages (renal care advice messages incorporating *APOL1* genomic risk information with conventional risk data) or conventional risk based advice messages to standard of care clinical decision support messages. During the first six months of year 1, the CLIPMERGE and Epic team at Mount Sinai will work with the Epic team at IFH to build HL7 interfaces customized between CRAE and the specific Epic version installed for IFH sites.

Reference and educational material. Upon presentation of a BPA, providers will have the opportunity to directly access reference content that further describes the evidence base for the CDS through a clickable link in the Epic SmartSet.

Sub-Aim 2.2. Development and usability testing of a library of evidence-based renal care advice messages customized for assessment of risk with and without *APOL1* G1 G2 risk allele information, and for adherence to practice guidelines for renal care in non-diabetic African ancestry participants with hypertension

Rationale. CKD awareness among participants and providers, appropriate use of tests for biochemical markers of CKD (creatinine and urinary albumin excretion) to screen for presence of CKD in those at risk, and appropriate use of pharmacological and life style interventions in those at risk for CKD progression are considered critical to improve CKD-related outcomes (ESRD, CVD, and mortality (24, 25). As summarized in the paragraph "**Synthesis: Poor adherence with renal care practice guidelines puts participants at risk for kidney failure"** at the beginning of the APPROACH section, major goals of practice guidelines for renal care in hypertensive participants remain unmet in clinical practice today. Blacks have higher prevalence of hypertension (41% vs. 28%), younger age of onset, and poorer control of hypertension than Whites (17). Blacks also have, a 2-3x the risk for developing CKD (12), and the adjusted prevalence rate for ESRD is 4.1-fold higher in AA when compared with Whites (14-16). The differences in CKD are most pronounced among those with hypertension. Thus, it is imperative to uncover new strategies to screen and engage AAs with hypertension into programs to improve BP control and participant outcomes.

The Kidney Disease Improvement Global Outcomes (KDIGO) evidence-based practice guidelines advise the appropriate use of tests for biochemical markers of CKD (creatinine and urinary albumin excretion) to screen for presence of CKD in those at risk, and appropriate use of pharmacological and lifestyle interventions in those at risk for CKD progression are considered critical to improve CKD-related outcomes (ESRD, CVD, and mortality (24, 25). Practice guidelines, including the Joint National Commission 7 (JNC7) guidelines, recommend specific medications (ACE inhibitors and ARBs) as preferred first line agents and more intensive blood pressure goal in participants with hypertensive CKD (9-11).

Several reports demonstrate that *APOL1* risk alleles are highly significantly associated with CKD attributed to essential hypertension in non-diabetic AASK participants, and the genetic association was most robust in individuals with progressive renal functional decline (22) (see our AASK Cohort data in Table 1). Because of the overwhelming strengths of the evidence, we propose to establish *APOL1* genomic risk status in non-diabetic AA participants and to incorporate the *APOL1* G1/G2 risk allele status in a recessive model together with conventional risk factors in CKD and CKD progression advice messages.

Aim III. Conduct a randomized trial assigning eligible participants to immediate genetic testing or delayed genetic testing arms in a seven (immediate testing) -to- one (delayed testing) ratio.

Sub-Aim 3.1: To examine whether increase in practice guideline-appropriate renal laboratory test ordering (renal care endpoint) will be achieved in *APOL1*-positive group vs *APOL1*-negative group.

Sub-Aim 3.2. To examine whether systolic blood pressure will decline more in the *APOL1*-positive group compared with *APOL1*-negative group.

2. ENDPOINTS

2.1 Primary Endpoints

The study has two primary endpoints, comparing patients who are *APOL1* positive (high risk) and *APOL1* negative at three months after enrollment. One primary aim is a renal care endpoint, the correct utilization, by clinicians, of urine albumin tests. The other primary aim is reduction of systolic blood pressure.

2.2 Secondary Endpoints

Secondary endpoints include differences between APOL1 positive participants in the intervention and participants in the control group, impact on primary outcomes at 12 months, psycho-behavioral differences of participants between groups and over time, clinician knowledge, attitudes and beliefs at baseline and 12 months, and differences in outcomes between those tested and not tested immediately.

3. STUDY DESIGN

3.1 Study Arms & Design

This is a prospective, multicenter, unblinded, randomized clinical trial (RCT) (**Figure 1**). The study was designed to randomize 2050 participants to immediate *APOL1* gene testing and return of results (ROR) (intervention) or delayed *APOL1* gene testing and ROR (control) in a 7:1 ratio. Outcome measures will be compared among three arms of the GUARDD study, the *APOL1*-positive and *APOL1*-negative intervention (immediate *APOL1* genetic testing and return of results) groups, and the control (delayed *APOL1* testing and return of results) group.

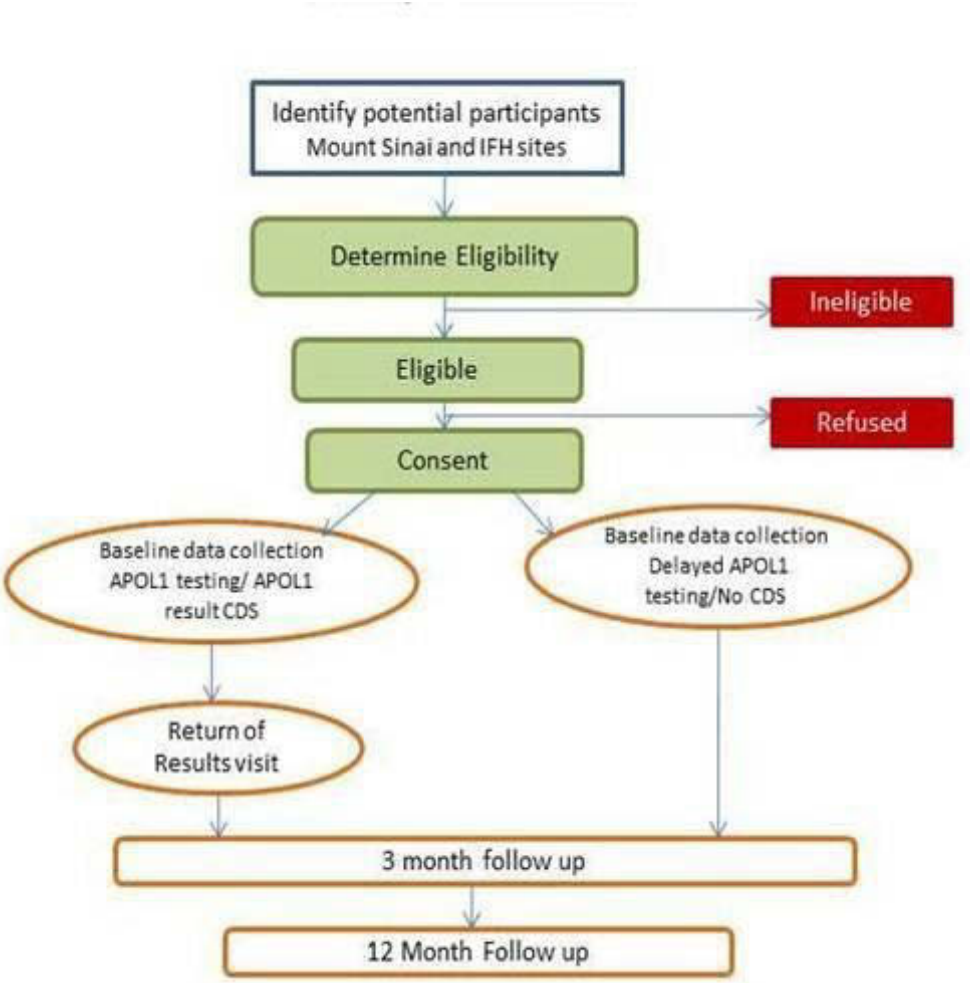


Figure 1. GUARDD study flowchart.

3.2 Randomization

Eligible participants will be randomized in a 7:1 allocation to Intervention (i.e., immediate *APOL1* gene testing and ROR to participant and provider) and Control arms (delayed *APOL1* gene testing and ROR to participant and provider) to optimize the proportion of participants with immediate *APOL1* genetic testing compared with delayed genetic testing at completion of study. Randomization will be stratified by clinical site with a random block size within site.

3.3 Blinding

GUARDD randomization assignments will not be blinded to any participants, providers or study personnel. To minimize bias in the measurement of the primary outcome, randomization assignments will only be revealed after baseline survey responses and blood pressure readings have been collected. Digital blood pressure devices (such as BpTru portable blood pressure machine (29)) will be used to measure blood pressure, and blood pressure will be measured as the mean of the second and third blood pressure readings for each participant at each study visit.

If a participant is referred, the Study Coordinator should check the REDcap database to ensure the participant is not already in the database and proceed accordingly.

Participant Recruitment

There are three main scenarios for recruitment:

- **Via recruitment letter:** Study Coordinators will be assigned participants (from the list of potentially eligible participants obtained through an Epic data run) and mail study recruitment letters to them. Letters are mailed in a bright blue envelope and postmarked with the GUARDD and clinic site logo to assist participants with recall and recognition. Participants can call us upon receiving the letter and they will then be screened for study eligibility. Study Coordinators will wait approximately 2 weeks after this mailing for a participant to return the letter refusing to participate, to call them, or to meet them at an upcoming clinic visit.
- **During a phone call:** If a participant does not return the refusal letter or contact us within 2 weeks of mailing, the Study Coordinator assigned to him/her will contact the participant by telephone. Using the recruitment phone script they will remind them about the letter that was mailed to them, introduce or reintroduce the study, screen them for eligibility, and answer any questions about the study.
- **During a clinic visit:** The Program Manager will receive a weekly list of which participants/potentially eligible participants have a scheduled clinic appointment and will notify the Study Coordinator assigned to that clinic site so s/he will plan to meet the participant at that time. The clinical Study Coordinator will discuss the study with the participant, screen them for eligibility, and answer any questions about the study.

Study Coordinators will then schedule all eligible and interested participants for a baseline visit. A baseline visit may occur at the time of recruitment (if approached at a clinic visit) or at a later date.

5.4 Screening Procedures

Study Coordinators will use a recruitment script during recruitment phone calls or clinic intercepts to inform the potential participant about the study and screen participants for eligibility using the study inclusion/exclusion criteria. If the participant is eligible and interested, a baseline visit will be scheduled that same day or for a future date.

5.5 Participant Consent Process

If a participant is interested and eligible, Study Coordinators will review the consent document at the start of the baseline study visit. Prospective research participants will have the opportunity to ask questions before providing written consent. Study Coordinators will provide the participant with a copy of the consent document. If the individual chooses not to sign the consent form, the Study Coordinator will inform him/her they are unable to participate in the study. The participant will also be provided the option to be contacted for future research.

5.6 Participant Discontinuation/Withdrawal from the Study

Participants may stop participating or withdraw from the study at any point in time. All information and data collected from the participant up to that point can be used in the study. Withdrawal of consent to participate in

trained in phlebotomy, collect 1 purple tops EDTA tube (approximately 3-5 mL) of venous blood from participants willing to provide a blood sample. If the Study Coordinator is not trained in phlebotomy, the participant will have their blood drawn by a trained phlebotomist. Participants will then be randomized to the Control or Intervention arm. Study Coordinators will label the tube with the participant ID, date of birth, sex and the date sample was collected, and follow the MOP for the collection, storage, and delivery of the sample to the laboratory.

Saliva Specimen: In the event that it is not possible to obtain a blood sample or participants prefer saliva collection, Study Coordinators will use an Oragene OG-500 kit to collect a saliva sample. They will label the sample and follow the saliva collection protocol for the collection, storage, and delivery of the sample to the laboratory as outlined in the MOP**.**

6.5 Specimen Transfer and Genetic Testing Procedures

Study Coordinators should store and directly transport specimens to the Mount Sinai Genetics Testing Laboratory, a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, according to procedures outlined in the MOP. Specimens will be accepted by the lab twice a week and processed on a weekly basis.

The *APOL1* G1/G2 genotype testing incorporates Polymerase Chain Reaction (PCR) and multiplex Allele Specific Primer Extension (ASPE) with Tm Bioscience's proprietary Universal Tag sorting system on the Luminex® 100 xMAP™ platform. Three SNP genotype in exon 6 are tested (RS73885319, RS60910145, RS71785313) to determine G1 and G1 allele status. To validate this genotyping method, at least three intra-assay and inter-assay runs involving 50 positive controls and 8 negative controls were performed. The positive control DNAs include samples which are heterozygous or homozygous for G1 and G2 genotypes. Negative controls are WT DNA for G1 and G2 alleles. Assays were 100% concordant reproducibly between the Luminex genotyping method and Sanger sequencing for each of the control samples.

6.6 Return of Genetic Results

Result reporting will occur approximately 1-4 weeks after the samples are obtained (see Fig. 1 Study flow chart). The laboratory will notify the study Program Manager of when results are ready to be returned. The Program Manager will in turn alert Study Coordinators. Return of results will be done by their assigned Study Coordinators. Study Coordinators will be trained by Randi Zinberg, Director of Mount Sinai Genetic Counseling Program, to return risk assessment results and recommendations. They will use a Return of Results Script for this visit. *APOL1* negative participants will have their tests results returned by phone (participants in the formative study said they did not want to come back in person for a negative results) and those that are *APOL1* positive will be scheduled for an in person return of results visit. If an in person return of results visit is not able to be scheduled for an *APOL1* positive participant, we will offer the participant the opportunity to receive their results over the phone. During return of results, the Study Coordinator will disclose the genetic test result, provide simple, clear information and use "speak back" or "teach back" technique to maximize participants' comprehension of their result. In addition to verbal ROR, participants will also receive lay explanations of their test results in writing and the educational booklet about *APOL1*, blood pressure and kidney

disease. *APOL1* positive participants will review the informational booklet at the time of their return of results, *APOL1* negative participants will receive their written test results and informational booklet in the mail.

If we are unable to return an *APOL1* positive test result to the participant for at least 3 months we will notify their primary care provider so that the result can be noted in their electronic health record and the participant can be notified of their results when they get in contact with their provider, even if that is after the study has ended.

All participants will be given the option to speak to a genetic counselor after their return of results in person or by telephone, at no charge. If a participant chooses to speak with a genetic counselor, the Study Coordinator will contact the genetic counselor on behalf of the participant, and the genetic counselor will then follow-up directly with the participants.

Once a result is returned to the participant, the Study Coordinator completes the corresponding fields in Redcap that prompts CLIPMERGE to fire a Best Practice Alert (BPA) in the participant's electronic health record the next time a primary care provider opens it. The BPA will pop up once per unique provider. A provider can choose to open the BPA and has the option of clicking on and viewing and printing information for the participant and information for him/herself. In addition to the BPA, the lab will also place a copy of the *APOL1* genetic test results in the participant's electronic medical record. Electronic Health Record Data Extraction

6.7 Electronic Health Record Data Extraction

Electronic health data relevant to the study endpoints will be pulled for the period of 12 months prior to randomization and 12 months after randomization for all enrolled participants.

Figure 2. *APOL1* positive BPA Alert