

Cover Letter

Reference: 5R01DK128207-05

Subject: Submission of Study Protocol and Statistical Analysis Plan to ClinicalTrials.gov PRS

Dear ClinicalTrials.gov PRS Administrator,

Please find attached the study protocol and statistical analysis plan for the following clinical trial for upload to the ClinicalTrials.gov Protocol Registration and Results System (PRS):

- **Study Title:** APOL1 Genetic Testing Program for Living Donors
- **Study ID:** 335133
- **NCT Number:** NCT04910867
- **Protocol Version:** Version 20
- **Publication Date:** March 30, 2026

Sincerely,

Akansha Agrawal, MD
Contact Principal Investigator
Northwestern University

Cc'd

Elisa Gordon, PhD, MPH, multiple Principal Investigator
John Friedewald, MD, multiple Principal Investigator

STU00214038

PROTOCOL TITLE:

Integrating a Culturally Competent *APOL1* Genetic Testing Program into Living Donor Evaluation
(STU00214038)

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Version 20

Summary of Changes

Protocol Section	Summary of Changes
24-Sources of Funding	Removing the following funding source- Northwestern Medicine Dixon Translational Research Grant- Innovation Award

1.0 OBJECTIVES

Apolipoprotein L1 (*APOL1*) risk variants may contribute to African American living kidney donors' even greater (3.3-fold) risk of end-stage renal disease post-donation than white living kidney donors. However, transplant physicians do not consistently use *APOL1* genetic testing or counsel African American living donor candidates about *APOL1*, which may undermine candidates' ability to give informed consent about donating and exacerbate health disparities in living donation and transplantation.

The objective of this study is to culturally adapt and evaluate the effectiveness of an *APOL1* genetic testing program for African American (AA) living donors (LDs) at two transplant centers serving large AA LD populations (Chicago, IL, and Washington, DC).

The specific aims are to:

Aim 1. Adapt the chatbot 'Gia' and transplant counseling to *APOL1* for use in routine clinical practice. We will adapt the clinical chatbot "Gia" (Genetic Information Assistant) and nephrologist counseling to ensure they are culturally competent—consistent with prior work—by engaging the AA community and experts in genetics, transplantation, and bioethics.

Aim 2. Evaluate the effectiveness of the *APOL1* testing program (intervention) on decisional conflict, preparedness, and willingness to donate in a pre-post design.

We hypothesize the *APOL1* testing program will:

H1: Decrease LDs' decisional conflict about donation

H2: Increase LDs' preparedness for decision-making about donation

H3: Not decrease LDs' willingness to donate

Aim 3. Evaluate the implementation of the *APOL1* testing program into clinical practice.

We will use the RE-AIM framework to longitudinally evaluate implementation outcomes (i.e., acceptability, appropriateness, feasibility, reach, adoption, and fidelity).

We hypothesize implementation will:

H4: Increase nephrologists' knowledge and skill in delivering counseling for *APOL1* and donation

H5: Increase LDs' satisfaction with informed consent about donation

2.0 BACKGROUND

Living donor (LD) kidney transplantation is the optimal treatment for patients with end-stage kidney disease (ESKD),¹⁻³ with greater patient survival and quality of life than deceased donor transplantation⁴⁻⁶ or dialysis.⁷⁻⁹ However, LDs have a higher risk of ESKD than non-LDs.¹⁰⁻¹² African American (AA) LDs have an even greater risk of ESKD than White LDs 15 years post-donation: 74.7 versus 22.7 per 10,000 LDs.^{10,11,13} Evidence suggests that genetic factors contribute to this greater risk. *Apolipoprotein L1 (APOL1)* risk variants (2 alleles) are significantly associated with ESKD, primarily in AAs (13% prevalence).¹⁴⁻¹⁸ AA LDs with two *APOL1* risk variants had significantly greater decline in post-donation kidney function than LDs with 0-1 risk variant,¹⁹⁻²¹ intensifying the transplant field's concerns to protect LD safety and ensure LDs' informed consent.²²⁻³⁰

Clinical practice guidelines advise "...considering *APOL1* genotyping in LD candidates with sub-Saharan African ancestors"^{31,32} and using shared decision making with LDs,³³ until the NIH APOLLO study of *APOL1* outcomes in LDs provides population-level data.³¹⁻³³ Transplant physicians are increasingly adopting *APOL1* testing;^{32,34} 49% used *APOL1* testing in 2019.^{33,35} However, they do not consistently inform LD candidates about *APOL1*, perform genetic counseling, or practice shared decision making with LDs.³³⁻³⁶ We showed this variation results from lack of knowledge and skill in *APOL1* counseling, and fear that *APOL1* testing will deter LDs from donating.³⁴ No studies report that they address AA LDs' cultural concerns about genetic testing.³⁷⁻⁴⁰

LDs are usually eager to donate to improve family or friends' health, and many are uncertain about donating.⁴¹⁻⁴⁵ The impact of *APOL1* testing and counseling on LDs' decision-making about donating is unknown. However, we previously showed that most (87%) AA LDs would have had *APOL1* testing, and fewer (61%) would have donated if they had two risk variants.⁴⁶ Thus, *APOL1* risks magnify LDs' decisional conflict about donating,⁴⁷ which can reduce LDs' likelihood to donate.⁴² However, genetic counseling can reduce decisional conflict.⁴⁸ Because LDs gain no direct medical benefit, protecting the safety via informed consent of this altruistic, at risk population is ethically required. Therefore, culturally competent testing and counseling are ethically essential to reduce LDs' decisional conflict and improve informed decisions about donation.

Hospitals increasingly use clinical "chatbots," mobile apps that use artificial intelligence to provide information to patients and relieve constraints on healthcare providers' time.⁴⁹ Chatbots can increase informed treatment decisions and reduce decisional conflict.^{50,51} However, no chatbot on *APOL1* is currently available. Invitae, a medical genetics company, offers a widely used chatbot, "Gia," that can be adapted to any condition. AA LDs' *APOL1* information needs identified in our prior work⁴⁶ will help adapt "Gia" to *APOL1*. We will also adapt effective genetic counseling training programs for physicians⁵²⁻⁵⁴ to focus on *APOL1* to address knowledge and counseling skill deficits about *APOL1* among nephrologists identified in our prior work.⁵⁵

The impact of this study will be the creation of a model for integrating genetic testing into clinical practice and increasing physicians' genomics literacy to improve patient informed consent. The study will also help transplant programs deliver *APOL1* genetic testing when the APOLLO study is done in ~5 years.⁶¹

3.0 STUDY ENDPOINTS

This overall project comprises three studies:

- **Study 1:** Adapting *APOL1* Testing Program Components
- **Study 2:** Evaluating Nephrologists' *APOL1* Counseling Knowledge, Skills, and Practice
- **Study 3:** Evaluating the Effectiveness of the *APOL1* Testing Program

Study 1

- There are no primary or secondary endpoints because this is a qualitative study.

Study 2: endpoints pertain to nephrologists and other relevant clinicians

The Primary Study Endpoint is:

- Number and quality of prescribed counseling practices performed by nephrologists (based on the observer checklist and electronic health record review)

The Secondary Study Endpoints are:

- Practical Knowledge and Self-Efficacy in Genetic Counseling
- Acceptability of Intervention Measure (AIM)
- Intervention Appropriateness Measure (IAM)
- Feasibility of Intervention Measure (FIM)
- Clinical Sustainability Assessment Tool (CSAT)
- Barriers and Facilitators to *APOL1* testing implementation
- Racial Attributes in Clinical Evaluation (RACE) scale
- Genetic Variation Knowledge Assessment Index (GKAI)
- Health Professionals Beliefs about Race (HPBR) scale

Study 3: endpoints pertain to living donors (LDs)

The Primary Study Endpoint is:

- LDs' Decisional Conflict about donation (DCS)

The Secondary Study Endpoints are:

- LDs' Preparedness for Decision-Making about donation (PDMS)
- LDs' willingness to donate
- LDs' Satisfaction with the informed consent process about donation

The Tertiary Study Endpoints are:

- LDs' Donation Decision Chosen (assessed via EHR review)
- LDs' Perceptions of Culturally Competent Counseling
- LDs' Decision Regret Scale (DRS)

Setting

Research activities will be conducted at the following study sites:

- Northwestern University (NU)
- Northwestern Memorial Healthcare (NMHC)
- Georgetown University (GU)
- Vanderbilt University Medical Center (VUMC)

4.0 STUDY INTERVENTIONS

There are two study interventions as part of this overall project:

1. **Intervention 1: “APOL1 Counseling Training Program for Nephrologists”**
 - Pertains to **Study 2**
2. **Intervention 2: “APOL1 Testing Program”**
 - Pertains to **Study 3**

Both interventions will be registered in [ClinicalTrials.gov](https://clinicaltrials.gov) prior to the study start.

Intervention 1: APOL1 Counseling Training Program for Nephrologists

The intervention entails educating and training transplant nephrologists to provide culturally competent counseling about *APOL1* in relation to donation for potential living donors.

This intervention entails training nephrologists in *APOL1* counseling. Training will be conducted by nephrologists, genetic counselors, an ethicist, and a cardiologist, and will cover practical knowledge (“know how”) and counseling skills. Counseling training will include training in shared decision making (SDM) as physicians lack training in SDM.^{215,216} Content will derive partly from our prior work identifying nephrologists’ knowledge and counseling skill deficits on *APOL1*¹⁵⁵ and on AA LDs’ and community members’ information needs.^{46,56,84} The Program will be delivered through 8 pre-recorded video presentations, lasting 2-3 hours over the course of 1-3 weeks.

We are expanding the target population who may receive the *APOL1* Counseling Training Program to include other clinicians who also evaluate living donor candidates (e.g., transplant surgeons, transplant nurses) as well as general nephrologists and general nephrologist fellows who treat living donors and kidney patients who may have *APOL1* risk variants. The rationale for expanding the target population is multi-fold: (1) having administered the Counseling Training Program to transplant nephrologists, we have demonstrated the feasibility in this clinical population. However, in the transplant context, oftentimes clinicians shift in their clinical responsibilities and cover for each other (e.g., surgeons performing clinical evaluations of living donors in lieu of nephrologists). Thus, expanding the clinician populations exposed to the Counseling Training Program will help to enhance the generalizability of using the Program in other clinician groups. (2) The number of transplant nephrologists who participated in the initial evaluation of the Counseling Training Program (n=14) was too small to detect statistically significant changes in knowledge and attitudes. Thus, increasing the clinician subject population will enable us to evaluate the Counseling Training Program with greater scientific rigor to determine if it can effectively increase knowledge and attitudes.

Given the need to increase our sample size to evaluate the effectiveness of the Counseling Training Program on knowledge and attitudes, we would also like to recruit transplant nephrologists, transplant surgeons, and transplant nurses from other transplant centers,

including Vanderbilt University Medical Center, University of Michigan–Ann Arbor, University of Wisconsin–Madison, University of Wisconsin–Milwaukee, University of Colorado–Denver, Yale University, Scripps Transplant Center, Beth Israel Deaconess Medical Center, Medical University of South Carolina, NYU, St. Louis University, Jackson Memorial Hospital–Florida, University of Arizona Tucson, University of California San Francisco, Duke University, Mount Sinai Medical Center, Baylor University Medical Center, NYU Stony Brook, Ohio State University, University of Chicago, Cedars Sinai, and Montefiore Medical Center, among others. We will use the same recruitment approach as described previously, i.e., reaching out via email (obtained from publicly facing transplant center websites) to potential participants to elicit their interest in participating and use an e-consent approach to obtaining informed consent (as an opt-out recruitment approach). We will rely on publicly available contact information for recruitment (e.g., transplant center websites, pubmed, Google, etc.). We will **not** obtain a list of names and emails from the organizations from which the potential participants are employed. Colleagues at each center may also forward our recruitment email to their transplant clinical colleagues to aid in recruitment for an opt-in recruitment approach.

At each of the sites that we decide to recruit from, we anticipate recruiting up to 75 clinicians at each site.

Intervention 2: *APOL1* Testing Program

The *APOL1* Testing Program aims to provide culturally competent genetic counseling and *APOL1* testing for AA LD candidates.

The *APOL1* Testing Program intervention components include:

- Asking all LD candidates about their ancestry: *APOL1* risk variants can be found in people with African genetic ancestry, but who do not identify as AA or African.¹⁵⁶ Asking all LDs about their ancestry will enable all LDs with African ancestry who might otherwise be missed to be included in the study. The 3 ancestry questions that will be used to screen potential participants for study eligibility, include:
 - “What ethnic/racial groups do you identify with?”
 - “Are you aware of any biologically-related family with African ancestry?”
 - “What is your ancestry?”
- Offering *APOL1* genetic testing to all LD candidates with African ancestry for *APOL1* risk variants after completing the first step of evaluation (i.e., medical health questionnaire) and clinical visit with the nephrologist who will provide pre-testing counseling. While *APOL1* testing is done in routine clinical practice on a case-by-case basis, the intervention component of this study is that all potential donors of African ancestry will receive *APOL1* testing.
- Genetic counseling will be provided about *APOL1*. Counseling is an essential initial step before the genetic testing process because it prepares and informs donor candidates of their treatment options. While nephrologists provide counseling in routine clinical practice about *APOL1*, the counseling is not currently culturally sensitive, and nephrologists have varied levels of knowledge and skill in delivering such counseling about *APOL1* specifically. Thus, the intervention component of this study is that the *APOL1* counseling that will be delivered before and after *APOL1* testing, is culturally sensitive, and delivered by nephrologists trained in *APOL1*, in two ways:

- A chatbot “Gia” will provide pre-test information about: basic genetic concepts, *APOL1* and kidney disease, risks and benefits of genetic testing, *APOL1* and living donation, and other topics, based on LDs’ information needs identified in our prior work.⁴⁷ It will not provide information about each LD’s own condition. The web-based app (accessible via participants’ cell phones or a study tablet) will be freely provided to LD candidates to access and use the chatbot.
- Nephrologists will provide pre-test counseling: Nephrologists will counsel donors about *APOL1* and encourage donors to undergo *APOL1* genetic testing, to normalize *APOL1* as part of the routine LD evaluation process.
- Nephrologists will provide post-test counseling: After donors’ *APOL1* test results have been entered into the EHR, Nephrologists will present *APOL1* test results in a culturally sensitive manner, counsel donors about the implications of the results for donor health post-donation, and engage in shared decision making (SDM) about donation with LDs who test positive for two risk variants.
- *APOL1* Transplant Program Policy: Both NU and GU transplant programs will develop a formal written policy about living donors donating with two *APOL1* risk variants to guide their shared decision making practices. The policy will be used to guide the clinical decision support.
- Integrating *APOL1* testing and counseling into the electronic health record (EHR): *APOL1* genetic test results will be returned from Knight Diagnostic Laboratories [<https://knightdxlabs.ohsu.edu/home/test-details?id=APOL1%2c+Sequencing>] via secure email and integrated into the EHR. EHR integration will occur at minimum at both NU and GU:
 - At NU: Because Epic does not permit the use of CareEverywhere Epic-compatible software for research purposes, NMHC IT team is not able to automate the integration of *APOL1* genetic test results from Knight Diagnostic Labs into Epic. Therefore, we will revert to the standard approach for integrating genetic test results into Epic which is to have the laboratory (KDL) fax the test results as a PDF directly to NMH. NMH’s clinical dedicated staff member who is already responsible for uploading faxed lab test results into Epic will be handling this step.
 - At GU, results will be scanned into GU’s EHR, Medconnect, as is standard practice.
- A culturally competent educational brochure on *APOL1* will be given by nephrologists to LD candidates of African ancestry during evaluation and will be made available in the transplant center waiting room.⁵⁶

NOTE: The final content of the chatbot pre-test counseling, the *APOL1* Transplant Program Policy, and the clinical decision support will be submitted as an IRB modification prior to delivering the *APOL1* Testing Program. The content of the nephrologist pre-test and post-test counseling will be developed in Study 2 as part of the *APOL1* Counseling Program for Nephrologists.

5.0 PROCEDURES INVOLVED

STUDY 1: Adapting *APOL1* Testing Program Components

Study Design

This study will employ a cross-sectional approach involving focus groups conducted in three iterative phases of user-centered design to elicit input on the *APOL1* Testing Program components, including: a) chatbot wireframes, content, design, and functionality, and b) nephrologist counseling about *APOL1* test results and shared decision making. Feedback will be gathered during focus groups to ensure that the chatbot and nephrologist counseling are culturally sensitive in their content and communication delivery.

Focus Groups

- A total of 10 focus groups will be conducted, 5 each at NU and GU. Each focus group will include, on average, 8 participants (range: 6-10).
- Focus groups will be conducted either: (a) in person at a conference room at NU or at the National Kidney Foundation of Illinois (Chicago, IL) and at GU or the Association for Multicultural Affairs in Transplantation headquarters (Richmond, VA); or (b) by telephone/Zoom meeting (due to COVID-19 restrictions).
- Each focus group will be conducted by an experienced moderator (Elisa Gordon, PhD, MPH or trained Research Coordinator) using a moderator's guide and will last approximately 90-120 minutes.
- The focus groups are designed to elicit feedback on the iterations of adaptations to the chatbot and nephrologist counseling program, including the shared decision making content. Focus groups will involve asking participants to answer open-ended questions and review and edit drafts of adapted materials. Participants will be asked for suggestions to enhance the intervention components to ensure that they are: informative and cover desired information needs, trustworthy, and culturally sensitive. Participants will be asked for suggestions to help minimize the possibility of "racializing medicine" when integrating the *APOL1* genetic test results into transplant counseling discussions about donation with live donor candidates.
- Research staff will take field notes during focus groups, and the focus groups will be audio-recorded.

Post-Focus Group Survey

- At the end of each focus group, participants will complete a post-focus group survey (via paper if in person, or via online if focus group is by telephone/Zoom). The post-focus group survey contains questions assessing further thoughts on the focus group topics and questions about demographics (e.g., age, gender). The survey will take about 10 minutes to complete.
- If the focus group is conducted online, REDCap will be used to host the online post-focus group survey. Each participant will be emailed a unique personalized URL to the survey midway through the focus group. This way, the research staff can check with participants at the end of the focus group to see if participants received the email with the URL. Use of the unique URL will enable research staff to determine which participants have completed the survey.
- Focus group participants will be compensated \$50 for their time. At NU, focus group participants will receive an e-gift card to a major retailer (e.g., Amazon, Walmart). At GU, focus group participants will receive a Nimblify Visa prepaid card. The Nimblify card will be mailed to the participant's home address if the focus group is conducted by Zoom/telephone. At NU and GU, if focus groups are held in person, participants will also be provided \$5 for parking, and refreshments during the focus group.

Community Advisory Board (CAB)

- A Community Advisory Board will provide input across all study aims. Dr. Gordon and Ms. Jacqueline Burgess-Bishop, CEO of the National Kidney Foundation of Illinois (NKFI) established a Community Advisory Board (CAB) to collaborate on this project. The CAB is comprised of 8 patient and community stakeholders who bring kidney disease, transplantation, donation, and African American religious, civic, and community perspectives to help adapt the genetic testing program.
- The CAB will convene 12 monthly meetings (in person, by telephone, or Zoom) in year 1 to provide feedback on: study design, enrollment, consent, and data collection procedures; genetic counseling content domains; and the shared decision making approach. The CAB will also ensure that the content, expression, tone, and delivery of the chatbot information and nephrologist counseling address both 'surface' (e.g., images of cultural expression, photos, colors) and 'deep' (e.g., values, beliefs, language shared by group members) cultural structures to increase receptivity to *APOL1* counseling by LDs of African ancestry.¹⁰⁵ Further, the CAB will identify ways to minimize the potential for the stigmatization of AAs and other groups from *APOL1* and *APOL1* genetic testing. The Table below shows the number of meeting occasions, meeting duration, and payment per meeting by study year.

CAB Compensation Plan			
Study Year	Meeting Occasions	Meeting Duration	Payment Per Meeting
1	12	2 hours	\$100
2	4	2 hours	\$100
3	4	1 hour	\$50
4	4	1 hour	\$50
5	4	1 hour	\$50

The American Association of Kidney Patients (AAKP)

The AAKP is a non-profit patient advocacy organization that has collaborated with Dr. Gordon on prior research studies, and would like to provide informal feedback on the Gia chatbot and nephrologist counseling training program, in much the same way as the CAB. The AAKP can provide review of these materials by its:

- Leadership team (President, prior President, and CEO)
- Ambassador program volunteer team comprised of 170 kidney patients, living donors, and family members who have been trained to do public speaking, give interviews with the media, participate in patient advisory boards, etc.

The NU research team will provide AAKP drafts of the materials for informal review and feedback. The AAKP will assist with the dissemination of study findings including through their use of the AAKP social media. No funds will be paid to the AAKP for their feedback assistance.

STUDY 2: Evaluating Nephrologists' *APOL1* Counseling Knowledge, Skills, and Practice

Study Design

This non-randomized single cohort pretest–posttest study aims to evaluate the *APOL1* genetic counseling training program on transplant nephrologists' practical knowledge about *APOL1*, self-efficacy in delivering *APOL1* counseling, and their engagement in shared decision making with live kidney donor candidates who have two *APOL1* risk variants. The study will also longitudinally assess nephrologists' perceptions of delivering the *APOL1* counseling program in terms of its acceptability, appropriateness, feasibility, fidelity, and sustainability. Nephrologists will partake in the following data collection activities, organized into 3 stages:

Stage 1. Refining the *APOL1* Counseling Training Program

Needs Assessment

- A final education needs assessment will be conducted about nephrologists' *APOL1* information needs and preferred format and content of the training program (e.g., webinar). Needs assessment interviews will be conducted by phone by a member of the research team. Interviews will last 15 minutes and will be audio-recorded.
- We will adapt the *APOL1* Counseling Training Program for nephrologists based on the needs assessment interviews, then obtain further feedback in focus groups to refine the content.

Nephrologist Focus Group

- Nephrologists will be invited to participate in one focus group (one per site) to elicit feedback on the *APOL1* counseling training program content, format, and design for further refinement prior to delivering the *APOL1* counseling training program. They will also provide input on the clinical decision support for the EHR.
- The focus group will last about 60 minutes and take place by phone or via Zoom. The focus group will be moderated using standardized approaches by Dr. Gordon, an experienced moderator, at Northwestern University. At Georgetown, the focus group will be moderated by Dr. Gordon or a Research Coordinator trained by Dr. Gordon. The focus groups will be audio-recorded.

Nephrologist Post-Focus Group Survey

- Nephrologists will complete an online post-focus group survey after the focus group ends. The post-focus group survey contains questions about demographics (e.g., age, gender) and nephrologists' experience with genetic testing and training. The survey will take 5 minutes to complete.
- REDCap will be used to host the online post-focus group survey. Nephrologists will be emailed a unique personalized URL to the survey midway through the focus group and research staff will check with participants at the end of the focus group to see if they received the email. Use of the unique URL will enable research staff to determine which participants completed the survey.

Stage 2. Delivering the *APOL1* Counseling Training Program***APOL1* Counseling Training Program for Nephrologists**

- The *APOL1* counseling training program for transplant nephrologists (intervention) will be delivered by nephrologists, genetic counselors, an ethicist, and a cardiologist (co-Investigators) via 8 pre-recorded video presentations, which will cover practical knowledge, counseling skills, cultural competency, and shared decision making.
- The *APOL1* Counseling Training Program will last approximately 2-3 hours and will be delivered over the course of 1-3 weeks.
- The *APOL1* Counseling Training Program will cover knowledge and communication skills regarding: (a) current *APOL1* data, (b) the risks of having two *APOL1* gene variants on living donor's kidney health, reproduction, and other family members, (c) the relative benefit to recipients of a living donor kidney transplant versus staying on dialysis, (d) how to frame communication about genetic risks as modifiable versus non-modifiable, (e) how to avoid genetic essentialism¹ by placing end-stage renal disease risk within its broader context of social determinants of health,² (e) how to address cultural and social values and beliefs in genetic testing in a culturally sensitive manner,^{3,4} (f) how to communicate the value of *APOL1* testing and meaning of positive test results for living donor clinical evaluation, (g) how to protect living donors' privacy and confidentiality with test results, the disposition of, and access to test results, as African American living donors and community members desire,⁵⁻⁷ and (h) how to engage in shared decision making about donation when living donors have two risk variants.
- The last video in the series will be a case study discussion by the video presenters (co-Investigators). At the end of the case study video, we will provide a secure, Northwestern-issued email address [Apol1TrainingModule@northwestern.edu] that nephrologists can use to email the video presenters with questions about the Nephrologist Counseling Training Program and related content. The video presenters will respond to their questions by email. Only the research team will have access to this email account.
- Online **pretest-posttest surveys** on the *APOL1* Counseling Training Program will be conducted immediately before and immediately after receiving the program. REDCap will be used to host the online pretest and posttest surveys. The training program learning objectives will be provided at the beginning of the online pretest survey. The surveys will take 5-10 minutes and will cover key knowledge and self-efficacy skills addressed in the Program.
- The *APOL1* Counseling Training Program will be provided through Northwestern University Feinberg School of Medicine's CME program and hosted on their Cloud CME website. After completing the Nephrologist Counseling Training Program, nephrologists and other clinicians will have the option to claim Maintenance of Certification (MOC) and Continuing Medical Education (CME) credit. If nephrologists choose to claim MOC credit, they will complete the MOC questions at the end of the posttest survey in REDCap and provide their ABIM Diplomate ID, their month and day of birth, and provide permission for their MOC completion information to be shared and transmitted to the Accreditation Council for Continuing Medical Education (ACCME). If nephrologists or other clinicians choose to claim CME credit, they will complete the CME questions on the CME program's website where the training program will be hosted (i.e., Cloud CME) after they complete the posttest and optional MOC questions.
- Several emails will be sent to the nephrologists or other clinicians during the *APOL1* Counseling Training Program intervention to provide them links for accessing the pretest/posttest surveys, the training program, and the website to claim CME credit. NU and GU nephrologists or other clinicians will receive the following email communications from research staff:

- Email with Pretest Link – to be sent soon after the nephrologist or other clinician consents to participate in the Study 2 *APOL1* Counseling Training Program. The purpose of this email is to provide the link to the pretest survey in REDCap.
- Email with Training Program Link – to be sent soon after the nephrologist or other clinician completes the online pre-test survey. The purpose of this email is to provide the link to the *APOL1* Counseling Training Program.
- Email Reminder – to be sent during the course of completing the training program videos. The purpose of this email is to let nephrologists or other clinicians know how many videos and how much time they have left to complete the training program.
- Email with Posttest Link – to be sent soon after the nephrologist or other clinician completes the training program. The purpose of this email is to provide a link to the posttest survey in REDCap.
- Email about CME credit – to be sent soon after the nephrologist or other clinician completes the online post-test survey and optional MOC questions. The purpose of this email is to provide a link to the CME website so that the nephrologists or other clinicians can claim CME credit if they choose to.
- We will track each nephrologist's or other clinician's progress through the *APOL1* Counseling Training Program so that we can email them the reminder email and send the email with the post-test survey link after they finish the training videos.
 - Only NU research staff will have access to the NU Feinberg CME Program's dashboard to track NU and GU nephrologists' or other clinicians' progress through the training program.
 - The CME dashboard will include the full names and email addresses of the nephrologists or other clinicians who are participating in the training program. Therefore, NU research staff will be able to view the nephrologist or other clinician participants' full names and email addresses.
 - While NU research staff will already know the names and email addresses of the NU nephrologists because they are NU study participants, NU had not originally planned to collect names and emails of GU nephrologists or other clinicians. Given this, language has been added to the GU Study 2 Nephrologist (and other clinician) consent form to inform GU nephrologists and other clinicians about NU research staff having access to view their names and email addresses for the purpose of tracking their progress through the training program.
- At NU, participants will be compensated \$250 in a virtual payment card, e-gift card, or via payroll (for NU nephrologists and clinicians) for their time, after they complete the Counseling Training Program posttest survey. At GU, participants will be compensated \$250 in a Nimblify Visa prepaid card, after they complete the training program posttest survey.
- We are increasing the compensation rate from the prior amount of \$50 to the new amount of \$250 because we have had low participation rates, and we need to increase participation in order to attain a large enough sample for evaluating the results and publishing our findings.
- The compensation of \$250 should not cause undue influence on clinicians' decisions about whether to participate in the study because transplant clinicians are extremely busy, and increasingly asked to complete research surveys and other data collection activities. Low compensation amounts do not make participation in research worthwhile per communication with many transplant nephrologists. The transplant nephrologist on our DSMB said that compensation amounts near \$500 would be reasonable to expect clinicians to take the time to complete surveys.
- Moreover, the Nephrology Counseling Training Program entails a longer investment of time and cognitive engagement than a simple survey because participation entails a

pre-test survey and posttest survey in addition to viewing 2.5 hours of educational videos. Thus, the compensation is commensurate with the time and energy involved in participation.

Stage 3. Delivering the *APOL1* Testing Program

Nephrologist Interviews

- Before nephrologists start applying the skills they learned from the *APOL1* Counseling Training Program to their clinical evaluation of live donor candidates, they will be interviewed using open-ended questions to assess their perceived organizational capacity as well as facilitators, barriers, and adaptations to implementing the *APOL1* counseling training program intervention. NU nephrologist interviews will be conducted by Dr. Gordon, an experienced interviewer, or a trained Research Coordinator. At GU, interviews will be conducted by a trained Research Coordinator. Interviews will be conducted in person, by Zoom, or by phone, last 30 minutes, and be audio-recorded.
- We will interview nephrologists 3 times:
 - Q4 - before Study 3 intervention implementation
 - Q6 - early after Study 3 intervention has been implemented
 - Q17 - before Study 3 implementation ends

Nephrologist Surveys

- After nephrologists begin to apply the skills they learned from the *APOL1* Counseling Training Program to their clinical evaluation of live donor candidates, they will be surveyed 4 times: the first 3 time points will use 3 validated surveys about their perceptions of the acceptability, appropriateness, and feasibility of delivering the *APOL1* counseling. The last time point will use 1 validated survey about nephrologists' perceptions of the sustainability of the *APOL1* counseling and testing program. The surveys will be conducted online or by telephone and will take a total of < 5 minutes to complete.
- Nephrologists will complete surveys at the following project time points:
 - Q4 before Study 3 intervention implementation
 - Q6 - early after Study 3 intervention has been implemented
 - Q8 - after 1 year of Study 3 intervention implementation
 - Q16 - after 3 years of Study 3 intervention implementation

Audio-Recordings of Nephrologist Post-Test Counseling about *APOL1* Genetic Test Results

- Research staff will coordinate with nephrologists to audio-record the nephrologists delivering their post-test counseling about *APOL1* genetic test results to live donor candidate study participants in person or by telephone. After the counseling sessions, research staff will listen to the audio-recordings and use an observer checklist to document the presence/absence and quality of nephrologists' counseling behaviors (as expressions of nephrologists' practical knowledge and skills). This data collection activity will serve to assess the fidelity of the *APOL1* counseling practices. Counseling sessions will likely last 10-20 minutes.

EHR Data Collection on Nephrologist Use of Clinical Decision Support

- We will collect data from the EHR on nephrologists' use of clinical decision support to document nephrologists' receipt of *APOL1* test results and delivery of *APOL1* post-test counseling (e.g., documentation of having called the living donor study participants to engage in post-test counseling).

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STUDY 3: Evaluating the Effectiveness of the *APOL1* Testing Program

Study Design

This study is a Type II effectiveness-implementation hybrid design, and entails a non-randomized, pre-post design. Data will be collected from participants at both NU and GU study sites during a control period prior to implementing the intervention, and during an intervention period as part of the *APOL1* genetic testing program. That is, the full population of live kidney donor candidates will be screened and recruited during both the pre-implementation (year 1, control arm) and implementation phases (years 2-5, intervention arm). Baseline and follow-up measures will be assessed to fully characterize the cohort and evaluate changes in outcomes over the study period.

Living donor candidates will participate in the following data collection activities:

1. Surveys (Control Arm + Intervention Arm)

- a) Baseline (first) surveys will be conducted:
 - a. In person in the living donor evaluation clinic at Northwestern University's transplant center, in a private location (e.g., conference room or patient exam room) during a routine period of downtime in the evaluation process (e.g., noon). For the Intervention Arm at NU, baseline surveys may be conducted over the phone following informed consent during telephone recruitment, or in person during clinic.
 - b. During in-person and virtual living donor evaluation clinics at Georgetown University:
 - i. In-person—in the living donor evaluation clinic at Georgetown University's transplant center, in a private location (e.g., conference room or patient exam room) during a routine period of downtime in the evaluation process.
 - ii. Virtual—via Zoom videoconference during the virtual living donor evaluation clinic hosted by Georgetown University's transplant center, in a private online “breakout” room during a period between visits with providers.
 - c. All living donor candidates in the control arm and in the intervention arm will receive Baseline surveys.
 - d. These surveys will assess outcome measures and demographics.
- b) The second and third surveys will be conducted by telephone, in person, or online*.
 - a. Only living donor candidates in the intervention arm will receive second and third surveys. No candidates in the control arm will receive these surveys.
 - b. These surveys will assess outcome measures, and process measures regarding experience and satisfaction with the chatbot and nephrologist counseling components.
- c) The Final (fourth) surveys will be conducted by telephone, in person, or online*.
 - a. All living donor candidates in the control arm and in the intervention arm will receive Final surveys.
 - b. The Final surveys will assess outcome measures.

*When scheduling a follow-up survey, research staff will offer participants the option to complete the survey online, if needed. The option for online surveys may facilitate participant retention among those who prefer to complete surveys online by themselves and when it may be more convenient for them. For study participants who we are not able to reach for their surveys, we will continue attempts to contact them up to 12 months following the timeframe for

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their final survey. For participants who we are not able to reach, who donated, and who have a 6-month or 1-year post-donation follow up clinic visit scheduled with the transplant clinic, research staff will coordinate with clinic staff to meet the study participant at the clinic about conducting their survey(s). If the study participant is scheduled for a televisit appointment (instead of an in-person visit), research staff will coordinate with clinic staff to call the participant after their televisit appointment.

- d) All surveys will last approximately 10-30 minutes each. All participants will be compensated \$20 for completing the Baseline survey, and \$25 for completing the Final survey. All intervention arm participants will also be compensated \$10 for each of the second and third follow-up surveys.

2. Chatbot Counseling Session Intervention and Meta-Data (Intervention Arm Only)

- a) After intervention arm participants complete the Baseline survey, the research staff will assist participants in accessing the chatbot on their smartphone or other personal electronic device (or provide the participant with a study tablet). A unique ID# will be assigned to each participant and that ID# will be entered into the chatbot for tracking each participant's chatbot use.
- b) The research staff will encourage the participant to use the chatbot for approximately 7-12 minutes.
- c) The chatbot will provide information about genes, *APOL1*, the risks associated with *APOL1* for living kidney donors, and the purposes of *APOL1* testing. The chatbot is designed to prepare users to provide informed consent for *APOL1* genetic testing.
- d) The HIPAA-compliant chatbot records meta-data about the use of the chatbot including: whether the chatbot was launched, the duration of use, types of questions asked, and information sought. These meta-data will be collected and analyzed in aggregate as part of a process evaluation of the intervention, e.g., measure dosage (time spent exposed to this part of the intervention).
- e) When intervention arm study participants finish using the chatbot, the research staff will provide participants with the URL, login ID#, and instructions for signing into the chatbot, in case participants would like to use it again at a later time.

3. Transplant Nephrologist Pre-Test Counseling Session and Audio-Recording

- a) At NU, and at GU's in-person clinics, after leaving the donor candidate's room, the research staff will notify the transplant nephrologist about which living donor candidates gave informed consent to participate in the study.
- b) For GU's virtual clinics, research staff will obtain written informed consent from participants prior to the day of their virtual living donor evaluation clinic, or on the day of their virtual clinic if staff are not able to reach potential participants or go through the consent process with them prior to the potential participant's virtual clinic. On the day of the clinic, the research staff will communicate via Zoom with the evaluation clinic team, which includes the nephrologist, and/or communicate via text with the nephrologist, to notify them about who gave informed consent to participate in the study.
- c) This notification will serve as a reminder for the nephrologists to engage in pre-test counseling about *APOL1* with the donor candidate study participants in the forthcoming session with the nephrologist that afternoon. **(Intervention Arm)**
- d) As part of the routine clinical evaluation, all study participants will then meet with their transplant nephrologist. The nephrologist clinic visit entails discussion of donation risks (including *APOL1* and *APOL1* genetic testing, on a case by case basis) as part of routine evaluation. **(Control Arm + Intervention Arm)**

- e) As part of the intervention, discussion of *APOL1* and *APOL1* genetic testing will occur with all intervention arm study participants. As part of the counseling session, nephrologists will provide the rationale for getting the *APOL1* genetic test and encourage intervention arm participants to get the *APOL1* genetic test. Counseling sessions typically last 10-15 minutes. The intervention component of the counseling is that it will be culturally sensitive and nephrologists will be trained about *APOL1* and its implications for living donors. **(Intervention Arm)**
- f) Nephrologists will email study participants a culturally sensitive educational brochure on *APOL1* during the counseling session, they will also be able to “share their screen” to display the brochure during the counseling if needed. The brochure will also be made available in the transplant center waiting room. **(Intervention Arm)**
- g) Research staff will coordinate with the nephrologists to audio-record their pre-test discussions with study participants. Research staff will use an observer checklist while listening to the recording to systematically evaluate the fidelity to which the nephrologist engages in counseling and shared decision making about getting *APOL1* testing. **(Control Arm + Intervention Arm)**

4. *APOL1* Genetic Testing – Saliva Sample (Intervention Arm Only)

- a) At NU, and at GU’s in-person clinics, immediately after donor candidate participants in the intervention arm meet with the nephrologist, research staff will ask participants if they wish to undergo *APOL1* genetic testing. Those participants who agree will initial the section of their previously signed written informed consent that pertains to the option of genetic testing. Directly after giving consent to *APOL1* genetic testing, research staff will assist the participant in providing a saliva sample in a private location of the clinic (e.g., conference room or patient exam room).
- b) For GU’s virtual clinics, immediately after donor candidate participants in the intervention arm meet with the nephrologist during their virtual evaluation clinic, research staff will join the participant’s individual Zoom breakout room and ask them if they wish to undergo *APOL1* genetic testing. Participants who agree will be emailed their signed written informed consent document through DocuSign, and they will initial the section that pertains to the option of genetic testing. *APOL1* genetic testing (via saliva swab collection) will occur when donor candidate participants visit MedStar Georgetown University Hospital in-person (e.g., for donor testing).
- c) At both sites:
 - i. Although genetic testing is done for research purposes, the results will be entered into the EHR. Giving a saliva sample for genetic testing is not a required part of this research study, but would strongly contribute to the scientific rigor and validity of the study.
 - ii. During *APOL1* genetic testing, participants will put their saliva sample into a small plastic tube, which is a non-invasive, inexpensive, and non-labor intensive approach for collecting DNA. The research staff will then depart the room.
 - iii. Research staff will follow established protocols for collecting genetic material through saliva samples and preparing the saliva samples for shipping using the DNA Genotek’s OGD-500 ORAGene saliva shipping containers [the U.S. Food and Drug Administration (FDA) granted general use 510(k) clearance to these containers for diagnostic testing in research, which will ensure research quality and regulatory compliance.]
 - iv. Research staff will ship each prepared sample using certified mail through the US Postal Service to Knight Diagnostic Labs for *APOL1* genetic testing.

5. Transplant Nephrologist Post-Test Counseling Intervention and Audio-Recording

- a) For Control arm participants, *APOL1* test results will be returned electronically and entered into the electronic health record (but not integrated with clinical decision support). **(Control Arm)**
- b) For Intervention Arm participants, *APOL1* test results will be returned electronically by Knight Diagnostic Laboratories and integrated into the electronic health records with clinical decision support at NU and GU. **(Intervention Arm)**
- c) Nephrologists will notify research staff in advance about when nephrologists plan to call participating living kidney donor candidates to provide counseling about their *APOL1* test results. **(Control Arm + Intervention Arm)**
- d) Phone or videoconference calls will be held in the nephrologist's private office in the clinic or in the nephrologist's remote office location (e.g., at the nephrologist's home).
- e) Research staff will assist nephrologists in audio-recording the transplant nephrologists' post-test counseling phone/videoconference discussion with all study participants. The research staff may either be in the transplant nephrologists' office to audio record the telephone discussion (on speaker setting) or the nephrologist will record the discussion (e.g., held via Zoom, other videoconference, or telephone) using a digital recorder, cell phone audio-recording app, or computer audio-recording software. **(Control Arm + Intervention Arm)**
- f) As part of routine evaluation: The post-test counseling discussion will cover the results of the *APOL1* test, if it was taken, and address the implications of the results for donation based on nephrologists current knowledge and understanding of *APOL1*, and will last approximately 10-15 minutes. **(Control Arm)**
- g) As part of the intervention: The post-test counseling discussion will cover the results of the *APOL1* test, if it was taken, address the risks of donating with two *APOL1* risk variants, provide emotional support, and apply the newly developed policy regarding shared decision making pertaining to *APOL1* and donation, and will last approximately 10-15 minutes. The intervention component of the post-test counseling is that it will be culturally sensitive and nephrologists will be trained about *APOL1* and its implications for living donors. **(Intervention Arm)**
- h) Research staff will use an observer checklist when they listen to the audio-recording to systematically evaluate the fidelity to which the nephrologist engages in counseling and shared decision making by discussing *APOL1* risks in relation to living donors' health post-donation.

6. Electronic Health Record (EHR) Review

- For all study participants (control arm and intervention arm), we will collect information from the EHR (e.g., electronic health record number, genetic test results, dates of nephrologist post-counseling sessions and genetic test result return, indicators of nephrologist use of CDS) for the purposes of documenting *APOL1* test results and CDS. *APOL1* test results are directly related to how the nephrologist engages in the counseling intervention and shared decision making, and may affect outcome measures of living donors' decisional conflict, preparedness, and willingness to donate.
- At NU, the electronic health record number [or medical record number (MRN)] for all study participants will be obtained in person from the transplant division clinical staff prior to looking in the medical record. This is a necessary step in order to ensure that the EDW analyst at NU can identify and review the correct medical record.
- At GU, the electronic health record number or medical record number (MRN) is provided in the clinical provider schedule. The provider schedule will be used as a tool to obtain the MRN to access the EHR. The MRN will be used to ensure that the research staff identify and review the correct medical record.

All Studies:**Private identifiable information will be collected on:**

- Participating living donor candidates via self-report for the purposes of tracking, sending e-gift cards, and/or follow-up data collection (i.e., names, email, and phone contact information).
- Transplant nephrologists via self-report for the purposes of tracking only (i.e., names, email, and phone contact information).

Audio-Recording

Audio-recording is a necessary part of this research. Digital audio-recordings (e.g., via smart phone recording software, Zoom meeting recordings, digital recorder, or computer audio-recording software) across all studies will be electronic audio files and transcribed in order to qualitatively analyze participants' discussions (e.g., interviews, focus groups) and/or provide a back-up to support data collection (e.g., for the pre-test and post-test counseling sessions). Electronic audio files will be stored on password-protected, encrypted servers and will be accessible to only research team members on password-protected computers. Electronic audio files recorded on digital recorders or encrypted cell phones will be downloaded from the device as soon as possible after the audio-recording is complete, and saved to secured, password-protected files on encrypted servers. Once audio files are saved to a secure file location, the files will be deleted from the device (e.g., digital recorder, cellphone). All electronic transcription files will be stored on password-protected computers, on password-protected servers, and accessible to only members of the research team. All paper data files (i.e., transcriptions) of digitally-recorded data will be labeled with codes instead of participant names, and will be kept in locked cabinets in the research team's offices at NU. All paper data files will be stored in the locked transplant research office at GU.

Data Disposition

Data collected for generalizable knowledge will not include private identifiable information. Documents containing identifiable patient information will be destroyed within seven years of study completion (per NIH guidelines) using electronic "shredding" software.

6.0 DATA AND SPECIMEN BANKING**Study 1: Adapting *APOL1* Testing Program Components**

- No data/biospecimens will be banked for future research.

Study 2: Evaluating Nephrologists' *APOL1* Counseling Knowledge, Skills, and Practice

- No data/biospecimens will be banked for future research.

Study 3: Evaluating the Effectiveness of the *APOL1* Testing Program

- No data/biospecimens will be banked for future research.

7.0 SHARING RESULTS WITH PARTICIPANTS

APOL1 genetic test results will be entered into the living donor candidate's EHR and will thereby be made available to participants' transplant nephrologists for clinical evaluation.

Participants will be able to learn about the status and results of the research study at any time. We will create a website that describes the study, provides updates on recruitment numbers, and posts the reference citations of all presentations and publications resulting from the study. We will provide the website URL on all consent forms for participants to access at any time. The website URL is www.Apol1consent.org.

8.0 STUDY TIMELINES

Study 1: Adapting *APOL1* Testing Program Components

- Focus Group = 90-120 minutes each
- It will take approximately 6 months to complete enrollment of study participants for Study 1.

Study 2: Evaluating Nephrologists' *APOL1* Counseling Knowledge, Skills, and Practice

Stage 1: Refining the *APOL1* Counseling Training Program

- Needs Assessment Interview: 15 minutes
- Nephrologist Focus Group: 60 minutes
- Nephrologist Post-Focus Group Survey: 5 minutes
- Each nephrologists' participation in this stage will last the time stated above.

Stage 2: Delivering the *APOL1* Counseling Training Program

- Nephrologist *APOL1* Counseling Training Program: 2-4 hours over the course of 1-4 weeks. The exact time and duration will be determined in Stage 1.
- Pre-test and Post-test Surveys: 5-10 minutes
- Each nephrologists' or other clinicians' participation in this stage will last the amount of time stated in the 2 bullets preceding this one.

Stage 3: Delivering the *APOL1* Testing Program

- Nephrologist Interviews: 30 minutes (3 times)
- Nephrologist Surveys: 5 minutes (4 times)
- Each nephrologists' participation in the study will last: nearly 5 years.

Study 3: Evaluating the Effectiveness of the *APOL1* Testing Program

- LD Surveys: 10-30 minutes each
- Chatbot Counseling Session: 7-12 minutes
- Collecting Saliva Sample for *APOL1* Genetic Test: < 1 minute
- Pre-Test Counseling Discussion/Audio-Recording with Nephrologist: 10-15 minutes
- Post-Test Counseling Discussion/Audio-Recording with Nephrologist: 10-15 minutes
- Each living donor candidate's participation in the study will last: 2-3 months.
 - It may last longer depending on the number of clinical tests that donor candidates need to do to become eligible as a living donor because our end point is 1 month after rule-out or donation.
 - It may last longer for participants who we are not able to reach for their follow-up surveys. We will continue to contact them up to 12 months after the timeframe for their last survey.

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- It will take approximately 4.75 years to enroll all living donor candidate participants for Study 3.

Overall

- The anticipated duration of the overall project is 5 years.
- The estimated date for the investigators to complete the study's primary analyses is March 31, 2026.

9.0 INCLUSION AND EXCLUSION CRITERIA

Study 1: Adapting *APOL1* Testing Program Components

Inclusion criteria for focus group participants

- Adults (ages 18+)
- Community members who identify as African American/Black, Jamaican, Barbadian, Grenadian, Brazilian from Salvador, Trinidadian, Panamanian, Honduran, Haitian, Garifunan, Palenque, Guyanese, Dominican, Peruvian, Belizean, and Native American, or are aware of having biologically-related family with African ancestry or have African ancestry
- Kidney transplant recipients who identify as African American/Black
- Living kidney donors who identify as African American/Black
- English-speaking
- Cognitively intact individuals
- All genders
- Pregnant and nonpregnant women

Exclusion criteria for focus group participants

- Individuals who do not identify as African American/Black and are not aware of having biologically-related family with African ancestry and do not have African ancestry
- The rationale for excluding people without African ancestry is that *APOL1* risk variants are predominantly found in African Americans and people who have African ancestry, thus there is little need to include people who do not identify as African American/Black.

Study 2: Evaluating Nephrologists' *APOL1* Counseling Knowledge, Skills, and Practice

Inclusion Criteria

- Transplant nephrologists (including transplant nephrology fellows)
- Other relevant clinicians e.g., transplant surgeons, transplant nurses, general nephrologists, general nephrology fellows
- Adults (ages 18+)
- English-speaking
- Cognitively intact individuals
- All ethnic/racial backgrounds
- All genders
- Pregnant and nonpregnant women

Exclusion Criteria

- None

Study 3: Evaluating the Effectiveness of the *APOL1* Testing ProgramInclusion Criteria

- Living kidney donor candidates who identify as African American/Black, Jamaican, Barbadian, Grenadian, Brazilian from Salvador, Trinidadian, Panamanian, Honduran, Haitian, Garifunan, Palenque, Guyanese, Dominican, Peruvian, Belizean, and Native American, or state that they have African ancestry or are aware of having biologically-related family with African ancestry
- Living kidney donor candidates may be directed or non-directed donors
- Adults (ages 18+)
- English-speaking
- Cognitively intact individuals
- All genders

Exclusion Criteria

- Individuals who do not identify as African American/Black and are not aware of having any biologically-related family with African ancestry and do not have African ancestry
- Only African Americans and people of African ancestry will be included because *APOL1* risk variants are predominantly found in African Americans and people who have African ancestry.
- Pregnant women cannot be living kidney donors

10. PARTICIPANT POPULATION(S) BY TARGET SAMPLE SIZE

The target sample sizes in the table below are rough estimates for Study 1 and Study 2. Because there is turn over in attending transplant nephrologists at transplant programs over time, and Fellows are also eligible for study participation over the course of the coming years, we revised the sample sizes at both sites.

The recruitment process at Northwestern is going slower than anticipated. The recruitment process at Georgetown is going faster than anticipated. Because of these fluctuations in recruitment rates, we increased the sample size at both sites as a precaution.

We also increased the sample size at both sites to ensure that we remain in alignment with our IRB protocol, and the revised total sample size is approximately 1000.

Site	Study / Group	Target Minimum Sample Population	Increased Sample size
NU	Study 1: Kidney Transplant Recipients/Living Donors/AA Community Members	40	50
	Study 2: Nephrologists and other clinicians	7	65
	Study 3: Living Donor Candidates	195	250
GU	Study 1: Kidney Transplant Recipients/Living Donors/AA Community Members	40	50
	Study 2: Nephrologists and other clinicians	5	70
	Study 3: Living Donor Candidates	195	300
	Study 2: Clinicians nationally	--	215
Total		482	1000

11.0 RECRUITMENT METHODS

Study 1: Adapting *APOL1* Testing Program Components

Non-probability sampling techniques will be used in Study 1. Purposive sampling will be used to select individuals with similar characteristics of interest (kidney recipients and donors of African ancestry) from broader populations who could answer the research questions and study objectives. Purposive, maximum variation sampling will be used to gain insights into kidney recipients' and living donors' perspectives by including diverse subgroups (e.g., sex, age).

We will use opt-out and opt-in recruitment approaches for Study 1 focus groups.

Opt out:

- We will recruit potential participants from the NU and GU transplant programs. Research staff will obtain lists of contact information and demographics (i.e., ethnic/racial background, date of birth, gender, and primary language spoken) of kidney transplant recipients and living kidney donors from:
 - NU's Electronic Data Warehouse (EDW), which is linked directly to the Epic medical record system
 - GU's OTTR transplant medical record system

Note: A partial waiver of HIPAA authorization will be requested to review the medical record information for purposes of recruitment only, as described in Section 22.0, "Protected Health Information (PHI and HIPAA)", below.

- Letters will be mailed and/or emailed to eligible potential participants to introduce the study.
- About 1 week later, research staff will call potential participants to assess interest in participating and to obtain verbal consent by using a telephone script.

Opt in:

- We will engage our Community Advisory Board (CAB), which is comprised of primarily African American community organization leaders in Chicago, IL, and in Richmond, VA, to help recruit African American members of the communities that their organizations serve. CAB members will distribute paper fliers and advertise the study through email, on their organizational membership listservs, organization websites, and on their organizations' premises.
 - Interested individuals will contact the research team via telephone or email.
 - Research staff will then:
 - i. Email interested individuals and request their phone number.
 - ii. Once staff have the individual's phone number, staff will call potential participants and use a telephone script to explain the study in greater detail, and then obtain verbal consent. Then, staff will schedule the individual for their preferred focus group date.
 - iii. Staff will thereafter request the participant's email in order to:
 1. share a copy of the verbal consent form
 2. send a Zoom invite for the focus group
 3. send the URL link to the post-focus group survey

- Additionally, CAB members include representatives from the non-profit collaborating organizations: The National Kidney Foundation of Illinois, Chicago, IL, The Gift of Hope Organ & Tissue Donor Network, Itasca, IL, The Association for Multicultural Affairs in Transplantation (AMAT) in Richmond, VA, and The National Kidney Foundation of Washington, DC. These organizations also have access to lists of kidney transplant recipients and living kidney donors in their geographic areas. CAB members will assist in recruiting recipients and donors via mailing fliers and/or sending e-mails with fliers to recipients and donors on their organizational lists to contact the research staff if they are interested in participating.

Study 2: Evaluating Nephrologists' *APOL1* Counseling Knowledge, Skills, and Practice

We will recruit transplant nephrologists and other clinicians by initially giving a presentation about the study and their potential involvement at the transplant division meeting, then the transplant nephrology meeting. The presentations at Northwestern and Georgetown will be arranged by Dr. Akansha Agrawal (Northwestern University) and Dr. Alexander Gilbert (Georgetown University). Additionally, we will contact other transplant centers by email (obtained from the organizations' public website) to elicit their interest in participating in the Counseling Training Program. Colleagues at each center may also forward our recruitment email to their transplant clinical colleagues to aid in recruitment. Research staff will follow up with nephrologists and other clinicians by email or telephone to obtain written informed consent. Research staff will send the nephrologists and other clinicians an e-consent form through REDCap or DocuSign to obtain online written informed consent.

Study 3: Evaluating the Effectiveness of the *APOL1* Testing Program

- At NU, we will recruit living kidney donor candidates in person in the transplant clinic private consultation room during living donor evaluation. Research staff will use a screening script to screen all living kidney donor candidates during the in-person clinic by using the 3 ancestry questions. Those donor candidates who indicate they have African ancestry, if interested, will be asked to provide written informed consent to participate in the study at that time.
- NU will also use another recruitment approach to reduce the amount of time in the clinic to perform research activities. As an alternative to recruiting living kidney donor candidates in the transplant clinic, we will approach donor candidates by phone in advance of their clinic visit to screen and ask for informed consent from potential participants. This alternative recruitment approach will involve the following steps:
 - We will use NU's transplant clinic schedule provided in the medical records system to recruit living kidney donor candidates who have an upcoming clinic visit.
 - NU research staff will email/mail a recruitment letter to donor candidates approximately 1-2 weeks before the donor candidate's scheduled clinic visit and/or NU's transplant clinic team will include a flyer about the research study in the donor packet that they email to all living donor candidates. The recruitment letter and flyer will mention the study and that research staff will contact the donor candidate by phone prior to their clinic appointment.
 - NU research staff will call donor candidates 3 or more days after emailing/mailling the recruitment letter/emailing the flyer—prior to their scheduled clinic—to screen and ask for informed consent from potential participants.
 - NU research staff will use the Recruitment Screening Script that includes the same 3 ancestry questions noted above to screen all living kidney donor

candidates over the phone. Donor candidates who indicate they have African ancestry, if interested, will be asked to provide written informed consent to participate in the study. NU research staff will email the donor candidate the consent form via REDCap and review the consent form with them during the call. If the donor candidate is unable to receive the email and/or review the consent form during the call, research staff will inform the donor candidate that they will review the consent form and obtain written informed consent at the time of the donor candidate's upcoming clinic appointment.

- NU research staff will ask eligible donor candidates who consent to participate in the study during the phone call if they want to complete the baseline (T1) survey over the phone at that time. Participants who do not complete the T1 survey during the phone call will complete the T1 on the day of their clinic visit.
- At GU, living kidney donor candidates attend an in-person clinic or a virtual clinic (via Zoom) for living donor evaluation. GU will recruit living kidney donor candidates using the transplant clinic schedule provided in GU's medical records system.
 - GU's living donor candidates will receive a flyer about the study in the donor packet that the transplant clinic team mails to all living donor candidates. The flyer will mention the study and that research staff may contact living kidney donor candidates prior to their scheduled clinic appointment.
 - When the scheduler in GU's transplant clinic speaks with donor candidates to set up their clinic appointments, the scheduler will mention to donor candidates that a research team member may call the donor candidate in advance of their clinic appointment to inform them about a research study opportunity.
 - Research staff will call donor candidates prior to their scheduled clinic to screen and ask for informed consent from potential participants. When research staff call the donor candidate, they will ask if they feel comfortable having the discussion via Zoom or phone, and then proceed with whichever method the donor candidate prefers.
 - GU research staff will use a screening script to screen all living kidney donor candidates who attend an in-person or virtual clinic by using the 3 ancestry questions. Those who indicate they have African ancestry, if interested, will be asked to provide written informed consent to participate in the study.
 - If recruiting over the phone in advance of the living donor candidate's clinic appointment, GU research staff will email the donor candidate the consent form via DocuSign and review the consent form with them during the call. If the donor candidate is unable to receive the email and/or review the consent form during the call, research staff will inform the donor candidate that they will review the consent form and obtain written informed consent at the time of the donor candidate's upcoming clinic appointment.
 - GU research staff will ask eligible donor candidates who consent to participate in the study during the phone call if they want to complete the baseline (T1) survey over the phone at that time. Participants who do not complete the T1 survey during the phone call will complete the T1 on the day of their clinic visit.
- During year 1, prior to intervention implementation, living kidney donor candidates will be recruited into the control arm.
- During years 2-5, when the intervention has been implemented, living kidney donor candidates will be recruited into the intervention arm.

- To enhance retention and community engagement, we will send text messages and/or email messages, make phone calls, and/or mail greeting cards (e.g., birthday cards) to current participants, as recommended by our CAB. We will ask participants at the T1 baseline interview if they agree to be contacted by text message, email, phone, and/or mail for the purpose of engagement during the interview. This engagement with study participants will occur on several occasions, between interview occasions and after completing participation in the study. Engagement will be designed to express care and concern about participants, check in with how they are doing, see if they have any needs that the team can help with, direct them to the study website for study updates, wish them happy birthday, offer the opportunity to answer questions, refer them to other resources to learn about *APOL1*, or congratulate and thank them for having completed the study participation and helping to make a difference. If participants express needs for resources to address personal issues related to social determinants of health, we will share links (e.g., via text/email) to helpful resources provided by our CAB. For example, one such resource is the website www.cedaorg.net, which is relevant to those seeking help related to housing services and utility bill assistance, among other services.

12.0 COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

Study 1: Adapting *APOL1* Testing Program Components

- Focus group participants will be compensated \$50 for their time right after completing the post-focus group survey. At NU, the \$50 will be provided as an e-gift card to a major retailer (e.g., Amazon, Walmart), and at GU,+ as a Nimblify prepaid Visa card. If focus groups are held in person, participants will also be provided \$5 for parking, and refreshments during the focus group.

Study 2: Evaluating Nephrologists' *APOL1* Counseling Knowledge, Skills, and Practice

- **Stage 1:** Needs Assessment and Focus Group: No compensation is provided.
- **Stage 2:** Counseling Training Program: Nephrologists and other clinicians will receive \$250 in compensation via payroll (NU), through a Nimblify prepaid Visa card (GU), or through an e-gift card or virtual payment for participating in the *APOL1* Counseling Training Program, after completing the pre-test/post-test surveys.
- **Stage 3:** Program Evaluation: No compensation is provided.

Study 3: Evaluating the Effectiveness of the *APOL1* Testing Program

- Living donor candidate participants will be compensated \$20 for completing the Baseline surveys, and \$25 for completing the Final surveys.
 - All intervention group participants will also be compensated \$10 for each of the second and third surveys.
- Compensation will be provided right after completing each of the surveys.
- Compensation will be provided in a virtual payment card or e-gift card at NU. The form of compensation is changing because the SVC card program is being discontinued in August 2024 at NU.
 - Participants will receive the plastic, bankcard-like card after completing the Baseline survey in person, pre-loaded with \$20.
 - After participants complete subsequent surveys, the same card they initially received will be loaded with the amount of compensation for each survey.
 - Instructions and information about using the Stored Value Card are provided in the informed consent form.
- Compensation will be provided as a Nimblify prepaid Visa card at GU.
 - Participants will be mailed the plastic, bankcard-like prepaid Visa card after completing the Baseline survey during their virtual living donor evaluation clinic. The card will be activated after the living kidney donor candidate calls the research staff to confirm that they received the card. Once activated, \$20 will become immediately available on the card to the participant.
 - After participants complete subsequent surveys, the same card they initially received will be loaded with the amount of compensation for each survey.
 - Instructions and information about the Nimblify prepaid Visa card are provided in the informed consent form as well as in the insert included with the Nimblify card.

13.0 WITHDRAWAL OF PARTICIPANTS

All Studies

There are no anticipated circumstances under which participants will be withdrawn from the research without their consent, for Study 1, Study 2, and Study 3.

Study 3: Evaluating the Effectiveness of the *APOL1* Testing Program

We will inform participants (in the written consent form) that they may choose to withdraw from the study entirely or partially (e.g., withdraw from surveys but allow for continued data collection from the medical record). We will inform potential participants (in the written consent form) that should they wish to withdraw from the study, they should notify the Principal Investigator in writing (via email or letter) of their wishes to withdraw. When participants withdraw, research staff will inform participants that no future data pertaining to them will be collected. As soon as participants withdraw, research staff will stop collecting data on the portion of the study that the individual withdrew from. We will inform potential participants (in the written consent form) that any data collected up to the point of withdrawal will be used by the research team.

14.0 RISKS TO PARTICIPANTS

Study 1: Adapting *APOL1* Testing Program Components

- Risks to study participants completing the focus groups are believed to be minimal. Most of the focus group questions are neutral.
- The topic might cause distress among participants, especially prior living kidney donors who are learning about the role of *APOL1* risk variants as a risk of kidney disease in living donors for the first time.
- Another risk is loss of confidentiality, through access to data by people who are not members of the research team. However, the likelihood of a breach of confidentiality is low, and minimized through the precautions the research team will be taking.

Study 2: Evaluating Nephrologists' *APOL1* Counseling Knowledge, Skills, and Practice

- A risk to nephrologist and other clinician study participants are believed to be minimal for completing the: a) needs assessment interview and focus group, b) *APOL1* Counseling Training Program and surveys, and c) delivering the *APOL1* counseling as part of the *APOL1* Testing Program and completing surveys and having counseling sessions audio-recorded. The survey and interview questions are neutral.
- A risk to nephrologist and other clinician study participants is loss of confidentiality, through access to data by people who are not members of the research team. However, the likelihood of a breach of confidentiality is low, and minimized through the precautions taken by the research team.

Study 3: Evaluating the Effectiveness of the *APOL1* Testing Program**1. Minimal risks**

Risks to study participants for completing the surveys and audio-recordings are believed to be minimal:

- Most survey questions are neutral, thus, the psychological impact of the surveys to participants is expected to be minimal.
- There is the possibility for breach of confidentiality and loss of privacy; this possibility is minimized through precautions taken by the research team.

2. Greater than minimal risk

Risks to study participants for providing a saliva sample for genetic testing are believed to be moderate:

- A risk is the loss of confidentiality, through access to data by people who are not members of the research team. However, the likelihood of a breach of confidentiality, is low, and minimized through precautions taken by the research team.
- There is the risk for genetic discrimination. Having the genetic test results become part of the participants' medical record may increase the risk to participants' loss of privacy. If released, the information could lead to life insurance discrimination, job, or social discrimination. Participants' insurance company may have access to this information, just like they would any other information that is in their medical record. However, federal law - Genetic Information Nondiscrimination Act (GINA), makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information.
- Living donor candidate participants who learn about their genetic risks of having two *APOL1* gene variants may experience psychological distress.
- Living donor candidate participants who learn about their genetic risks of having two *APOL1* gene variants may be ruled out from donating.
- Risks may also be social and cultural: *APOL1* testing might be perceived or experienced as stigmatizing to the African American community.
- Not undergoing *APOL1* genetic testing and thus not knowing if one has two *APOL1* risk variants also has risks. It could mean that the participant will not have enough information to make an informed decision about donating.
- Participants' future relationships with family members, and/or the recipient, could be affected in as yet unknown ways.

15.0 POTENTIAL BENEFITS TO PARTICIPANTS

Study 1: Adapting *APOL1* Testing Program Components

Among focus group study participants, there is no anticipated direct health benefit.

Study 2: Evaluating Nephrologists' *APOL1* Counseling Knowledge, Skills, and Practice

- Stage 1: Transplant nephrologists participating in the needs assessment and focus group will not directly benefit from study participation.
- Stage 2: Nephrologists and other clinicians will very likely directly benefit from participating in the *APOL1* counseling training program. Specifically, they will likely gain new knowledge and skills for counseling live kidney donor candidates about *APOL1* in a culturally competent manner. These benefits will likely last for a long time as nephrologists and other clinicians practice their newly learned skills over time.
- Stage 3: Nephrologists delivering *APOL1* counseling as part of the *APOL1* Testing Program will not directly benefit from study participation.

Study 3: Evaluating the Effectiveness of the *APOL1* Testing Program

Living donor candidate participants may directly benefit by: a) receiving genetic information about their personal risks of future kidney failure post-donation, and b) receiving culturally competent counseling that helps donor candidates to better understand their risks in relation to the prospect of donating. Both genetic information and counseling are expected to reduce decisional conflict and help donor candidates make an informed decision about donating, which has a direct health impact.

16.0 DATA MANAGEMENT AND CONFIDENTIALITY

Training and Data Security – for All Studies:

- All research staff have been or will be certified in the responsible conduct of research by using the on-line Collaborative Institutional Training Initiative (CITI) training course. Dr. Gordon will provide the research staff at both sites with an orientation and training program in science and research methods that entails reviewing the study protocols and research methods (i.e., recruitment, administering surveys), data entry processes and data management, and the necessity for and approaches used to maintain routine communications with Dr. Agrawal, Dr. Gordon, and the research team to complete the study goals.
- The Community Advisory Board (CAB) members will be encouraged, but are not required, to complete the online CIRTification program that is tailored to the unique roles of community research partners and satisfies the Human Subject Protection training requirements. Note that the CAB is not engaging in human subjects research (e.g., they are not obtaining informed consent, collecting data, or analyzing identifiable data). Rather, CAB will be reviewing de-identified summaries of qualitative and quantitative data.
- Only authorized research staff will be able to access the study databases. The research staff has considerable experience collecting and managing confidential study participant information. We will adhere to HIPAA requirements for protecting patient privacy. Participants' identifying information is needed for the purpose of tracking financial compensation for participation and contacting individuals for subsequent data collection activities. All participants' names and identifying information will be coded to ensure confidentiality. All study participants will be given a unique identification number, which will be used on all paper documents and electronic data files. The only linkages between participants' identifying information and their identification numbers will be kept confidential in a minimal number of computer databases. All identifying information collected at both sites will be kept onsite; the research staff will have daily access to the study participants' identities to foster communication. To transmit data files securely, we will encrypt emails using the "[secure]" tag in the subject line of emails. All data collected will be kept on password-protected computers, on password-protected servers at Northwestern University, Georgetown University, and Vanderbilt University Medical Center, with access only to the Project Investigators and research staff.
- All identifying information will be kept separate from the datasets in digital and paper forms to ensure confidentiality. Electronic documents will be saved in password-protected, encrypted files. Password authentication will be enforced, and passwords will be changed on a quarterly basis and only authorized personnel will have access to password protected files. All paper data files and physical copies of digitally-recorded data will be labeled with codes instead of respondent names, and will be kept in a locked cabinet in the research team's offices. Electronic audio files will be stored on the computer server and will be accessible to only the research team on an encrypted server. Any documents containing identifiable patient information will be destroyed within seven years of study completion (per NIH guidelines) or IRB lapse using electronic "shredding" software. Final analyses will be presented in the aggregate, and no individual, patient-level identifiable data will be shared. No identifying data about participants will be publicly released or reported in publications resulting from this study.

Storage of Saliva Samples & Genetic Test Results

- Shipments of saliva samples will be shipped to Knight Diagnostic Laboratories.
- The shipments require a requisition form that specifies the participant's ethnicity. The participant's ethnic background will have been previously obtained through live kidney donor candidates' self-report at the beginning of the live kidney donor evaluation process.
- The research staff, Knight Diagnostic Laboratories, and the transplant nephrologists will have access to the participant's ethnicity, which will have been linked to living donors and maintained in the electronic health records.
- The saliva samples are consumed by Knight Diagnostic Laboratories in the process of extracting DNA to generate the genetic tests. Thus, no saliva samples will remain.
- The DNA and genetic test results are retained by Knight Diagnostic Laboratories forever and stored using a de-identified number. Thus, no personal identifier is used.
- The genetic test results will be integrated into NU's Epic by secure email, based on algorithms established by the NMHC, and into GU's Medconnect.

Statistical Design and Power

Study 1: Adapting *APOL1* Testing Program Components

Qualitative Analysis

All audio-recorded focus groups (Studies 1 and 2) and interviews (Study 2) will be transcribed and analyzed for themes emergent from the data^{228,229} using the constant comparison²³⁰ and inductive and deductive (e.g., CFIR) coding methods.²³¹ The research team will use an iterative process to independently review and openly code the first set of one to three transcripts. After coding each set, the research team will hold analytic retreats to compare codes and resolve discrepancies to reach consensus in code definitions to establish the codebook.²³² All transcripts will be independently coded until establishing inter-rater reliability ($Kappa > 0.80$).²²⁹ The coding scheme will be revised to adjust for new responses, with modified codes applied to prior transcripts, until reaching thematic saturation—when no new themes emerge from the data.¹⁹⁰ Multiple coders and inter-coder agreement checks will increase rigor and reliability of the codebook.²³³ Qualitative data analysis software (NVIVO) will aid in coding. We will increase the rigor and reproducibility of qualitative findings via: intermittent member checks with focus group and CAB members, and nephrologists will increase credibility. Using thick description and an audit trail will increase dependability and transferability. Self-reflexivity and triangulation will increase confirmability.²³⁴ Results from Study 2 interviews will be used to understand implementation processes, and help contextualize Study 3 quantitative results.

Study 2: Evaluating Nephrologists' *APOL1* Counseling Knowledge, Skills, and Practice

We plan to enroll a total of $n=12$ transplant nephrologist attending physicians [and approximately 20 nephrologist fellows for this study]. We will also enroll an additional $n=200-300$ other clinicians (e.g., transplant surgeons, transplant nurses, general nephrologists and general nephrology fellows). The effectiveness of the nephrologist counseling training program will be assessed primarily by comparing the counseling behaviors delivered between nephrologists counseling LDs in the control arm (prior to counseling training) versus intervention arm (after counseling training). We will use a fidelity measure; fidelity has 2 dimensions: (1) adherence (quantity of prescribed activities provided), and 2) quality (a Likert rating of how well that activity was provided). This fidelity measure will enable the examination of the difference between high and low quality fidelity and high and low adherence (2×2). We will compute a score for each prescribed checklist activity. Each prescribed behavior on the observer checklist will be evaluated as present/absent (score: 1 vs. 0). The behaviors documented as present will be evaluated in terms of their quality on a 5-point Likert scale (i.e., excellent, very good, good, fair, poor). The fidelity measure will use both adherence and quality metrics to generate a score (0-5) for each prescribed behavior. Each prescribed behavior's score will be compared by the nephrologist's sex/gender. We will also assess the association between the fidelity scores and the Study 3 score of the effectiveness of the intervention (decisional conflict), and by transplant program or individual nephrologist differences, using correlations and regression analysis (e.g., ANCOVA).

The effectiveness of the nephrologist counseling training program will also be assessed secondarily via paired tests of pre-post scores of validated surveys assessing practical knowledge and self-efficacy in counseling amongst all nephrologists and other clinicians. Descriptive statistics (means) will be used to summarize pre- and post-test survey data. Given the small sample size, we will assess increases in practical knowledge and self-efficacy in counseling skills through a Wilcoxon signed-rank test to compare the number of correct answers on the pre-test to the number of correct answers to the same questions on post-test. While we anticipate being underpowered to detect reasonable differences in scores, descriptive statistics summarizing changes in scores will be used to evaluate trends.

Study 3: Evaluating the Effectiveness of the *APOL1* Testing Program

Descriptive summaries will be generated for all data including means and standard deviations or medians, interquartile ranges and ranges for continuous data, and tables of counts and frequencies for categorical data. Graphical summaries (e.g., histograms, boxplots) will be used to assess distribution shapes and evaluate transformations to improve normality. To evaluate potential differences in LD demographic and clinical characteristics before and after implementing the *APOL1* intervention, summary statistics will be compared for LDs in the control and intervention enrollment periods within each center.

Analyses for our primary hypothesis will employ a linear mixed effect model with fixed effects for arm (pre or post implementation) and study period, with a random center effect. The random center effect will allow for separation of within- and between-center variance estimates and account for the clustering of observations within centers. The primary outcome, decisional conflict, will be measured by the Decisional Conflict Scale (DCS), and will be treated as a normal, continuous outcome. Modeling approaches will consider statistical adjustment for baseline measure of DCS, and other LD level demographic and clinical characteristics, in particular for characteristics that differ for LDs within a center before and after implementation. The multivariable approach to analyses will allow for inclusion of potential confounders, or particular importance given the non-randomized design. Sensitivity of intervention effects to

confounder adjustment will be reviewed. Analyses will be performed under an intent-to-treat framework and will be based on complete cases analyses. Missing data will be explicitly described and multiple imputation may be considered, assuming appropriateness of assumptions.

Primary analyses for our secondary hypothesis will employ similar methods as in Aim 1a, for the secondary outcomes: preparedness for decision-making, satisfaction with informed consent, perception of culturally competent counseling, and decision regret scale. A generalized linear model will be employed for decision chosen (donated/not donated) with logit link and binomial distribution. Primary analyses for the tertiary hypothesis will be conducted under a non-inferiority framework. Specifically, we will estimate a confidence interval for the difference in medians to compare the willingness to donate between the pre-implementation and implementation periods. If the lower limit of a two-sided 95% confidence interval is within the margin of non-inferiority, we will have evidence that the *APOL1* counseling intervention does not meaningfully reduce the willingness to donate. We will assume a non-inferiority margin of 1.5 units, which reflects a negligible difference in scores. Unless otherwise specified, all analyses will assume a two-sided type one error rate of 0.05.

Power considerations were based on assuming enrollment of 56 participants in the 10-month pre-implementation period and 240 in the post-implementation period for a total of 296. Methods for sample size estimates were based on a simplified comparisons of mean DCS between pre- and post-implementation periods. Necessary sample sizes were then inflated to account for multivariable model and to account for loss-to-follow-up, to ensure adequate power. Our proposed sample size will provided 80-90% power, with a two-sided type I error rate of 0.05, to detect differences in the mean DCS between arms ranging from 5.0 to 7.7, assuming standard deviations ranging from 12 to 16. Thus, our proposed sample size will provide adequate power to detect small to medium Cohen's D effect sizes. As similar studies have observed even larger effects, we anticipate seeing differences of at least this magnitude in our study. Power considerations were based on a simplified two-sample t-test; however, sample sizes were inflated upward by a factor of $1/(1-R^2)$ for planned multivariable models, resulting in a necessary sample size of 370. We have assumed an R^2 of 0.2, as an estimate of the square of the multiple correlation coefficient of the predictor of interest regressed on all other variables likely to be included in the model. Finally, we inflated our sample size to account for 5% attrition, thus we plan to enroll a total of 74 participants in the control arm and 316 in the intervention arm. Given our feasibility estimate of enrolling 86 per year over 4.33 years, our anticipated sample size should provide adequate power to detect clinically meaningful differences.

For the tertiary hypothesis, the proposed sample size will also allow for construction of a confidence interval around the difference in the mean willingness to donate score with adequate precision to claim non-inferiority if the lower limit of the confidence interval does not intersect with the NI margin. We have assumed a confidence interval centered between 0 and -0.2, 90% power, a one-sided type 1 error rate of 0.025, standard deviations of 2.660 in both groups, and an NI margin of 1.5 units.

The planned subgroup analyses will consider assessment of living outcomes of Decisional Conflict, Preparedness for Decision Making, Willingness to Donate, Satisfaction with the Informed Consent Process, and Decision Regret, by sex as a biological variable and age groups. These analyses will be deemed exploratory in nature, as we may not be adequately powered to detect differences within these subgroups.

16.0 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

Study 1: Adapting *APOL1* Testing Program Components

Not applicable.

Study 2: Evaluating Nephrologists' *APOL1* Counseling Knowledge, Skills, and Practice

Not applicable.

Study 3: Evaluating the Effectiveness of the *APOL1* Testing Program

Plan for Data and Safety Monitoring

- A Data and Safety Monitoring Board (DSMB) will be established to monitor data quality and safety for the *APOL1* Testing Program clinical trial. The DSMB will be comprised of voting members including a biostatistician, an expert in genetic causes of kidney diseases and *APOL1*, an expert in ethical and policy issues in human genetics and genomic research, and an expert in behavioral interventions to increase living donation among African Americans.
- The study team will perform centralized monitoring through Data and Status Quality Reports (DSQRs) and REDCap reporting features. Reports will include adverse event (AE) and serious adverse event (SAE) data.
- Depending on the amount, quality, and findings of data summarizations for study sites, study investigators may conduct on-site targeted monitoring visits.

Plan for Reporting Data to the IRB and Sponsor

- DSMB annual reports will be forwarded to the IRB by Dr. Agrawal and to the NIH by Dr. Gordon.
- Dr. Agrawal will be informed of SAEs and unanticipated problems potentially related to the study, as soon as they occur, by the study coordinator. Dr. Agrawal will notify Dr. Gordon (grant PI) who will notify the NIDDK (study sponsor) and the DSMB, within 48 hours of becoming aware of the event.
- Dr. Agrawal will be responsible for reporting SAEs and unanticipated problems to the IRB within 5 business days of becoming aware of the event. The IRB will forward its report of the SAE to the NIDDK.
- Results of on-site targeted monitoring visits will be communicated to Dr. Agrawal, and this communication will be shared with the NU IRB, NIDDK, and the DSMB.

Frequency of DSMB Meetings

- DSMB meetings will be conducted at least once each year, and in response to a safety event, or as ad hoc meetings, as requested by the DSMB Chair.

Data to be Reviewed

- Data and Status Quality Reports (DSQRs) will include the following study data, in aggregate form, and may evolve throughout the course of the study to include additional data:
 - Baseline information – screening and consent, enrollment, demographics
 - Primary and secondary response variables
 - Adverse events (AEs)/serious adverse events (SAEs)
 - Additional data collected for each AE includes: outcome(s)/action(s) taken, start and resolution dates (AE duration), expectedness, relatedness to training, and criteria for determination of SAEs
 - Other pre-specified response variables and/or covariates

- Items anticipated for DSMB review include: safety concerns, interim/cumulative data for study related AEs and effectiveness according to pre-established statistical guidelines; data quality, completeness and timeliness; performance of individual centers; compliance with goals for recruitment and retention, including participation of women and minorities; protocol adherence; factors that may affect the study outcome or compromise confidentiality (protocol violations, unblinding, etc.); and external factors such as scientific or therapeutic developments that may impact participant safety or ethics of the study.

How Safety Information Will be Collected

- AEs will be documented on case report forms (CRFs) and entered electronically into REDCap.
- SAEs will also be entered into REDCap, and in addition, a separate SAE narrative form will be completed.
- Targeted on-site visits may be conducted to review study procedures, documentation, and data completeness and accuracy, as determined by study investigators.
 - Study investigators will conduct the targeted monitoring visit and complete an accompanying site monitoring visit report to indicate findings and recommend corrective actions.

Frequency of Data Collection and Start of Safety Data Collection

- Safety data collection will begin as soon as data collection starts.
- Data reports (DSQRs) will be produced and reviewed weekly, on average. Once systems are in place, reports may be updated in real-time and can be reviewed more frequently as needed.

Who Will Review the Data

- The PI and study staff will review DSQRs weekly; study staff will ensure appropriate data entry, such as AEs and SAEs into REDCap.
- The PI and blinded physician outcome adjudicators will review SAEs.
- The DSMB will review data, reports, and safety events.

Frequency of Review of Cumulative Data

- Survey, medical chart review, and observation checklist data will be reviewed on an ongoing basis, as they are collected.

Statistical Tests for Analyzing the Safety Data

- There will be no formal interim analysis for efficacy or futility. The PI will rely on guidance from the DSMB regarding modifications of the study protocol and suspension or early termination of the study due to safety concerns, inadequate performance, or rate of enrollment.

Conditions that Trigger an Immediate Suspension of Research

- Reasons for suspension or discontinuation of study procedures at a site will include:
 - Safety or ethical concerns regarding site procedures
 - Major data quality or completeness issues that make continued enrollment of follow-up infeasible
 - External study or clinical information that make continuation of the protocol unethical
- At the study or site level, the study PI and NU IRB each reserve the right to suspend or discontinue the study at any time for safety, ethical, or practical concerns. The DSMB

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reserves the right to recommend study suspension or discontinuation as well, and the PI must communicate recommendations from the DSMB to the site and NU IRB with decisions and justification for choosing to follow (or not follow) the recommendations.

17.0 PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

- In the event that focus group participants express distress, the research staff will inform the participant about the option of speaking with the transplant psychiatrist, Dr. Franklin (Other Significant Collaborator) at Northwestern University, and the independent living donor advocate at Georgetown University. If the participant agrees to it, the research staff will put the participant in touch with these healthcare providers by giving the healthcare provider's contact information to the participant and/or asking the healthcare provider to reach out to the participant.
- Genetic counselors will be available, as a 'safety net', should living donor candidates need further counseling.
- We will inform eligible LD participants about laws that can protect participants from certain types of discrimination during the informed consent process. Specifically, we will describe the federal Genetics Information Nondiscrimination Act (GINA) of 2008, which offers protection from discrimination based on genetic information by employers and health insurance companies.
- We will inform eligible LD participants that the research team has worked with the community to identify ways to communicate about *APOL1* that minimizes the chances of conveying stigmatizing language during *APOL1* nephrologist counseling discussions.
- We will adhere to HIPAA requirements for protecting patient privacy. Participants' identifying information is needed only for the purpose of tracking financial compensation for participation.
- To protect confidentiality, at the beginning and end of the focus group, we will encourage all focus group participants to not share personal details about others after the focus group.
- All participants' names and identifying information will be coded to ensure confidentiality. All study participants will be given a unique identification number, which will be used on all paper documents and electronic data files. The only linkages between participants' identifying information and their identification numbers will be kept confidential in a minimal number of computer databases. All potential identifiers will be kept on a secure, password protected server accessible only to key study personnel. All identifying information collected at Northwestern University will be kept onsite.

The following individuals on the research team are permitted to access sources of information about the participants:

- Dr. Gordon – all sources of information on the NU server
 - Dr. Gordon will maintain an Affiliate appointment at NU, which holds the same privileges as an Adjunct appointment (e.g., access to NU email, NU REDCap data, FSM shared drive files).
- Dr. Agrawal – all sources of information on the NU server
- NU Research Study Team Members – all sources of information on the NU server

The following will be included as data:

- Consent forms
- Audio recordings of interviews
- Audio recordings of focus groups

- Audio recordings of pre-test and post-test counseling
- Transcriptions of interviews
- Transcriptions of focus groups
- Observation check-lists of pre-test and post-test counseling
- Interview hand-written notes
- Focus group hand-written notes
- Interview demographics
- Focus group demographics
- REDCap, Excel, or SPSS of data entered from interviews and surveys and EHR data collected
- Excel tracking databases of participants and their contact information/consent status
- Financial tracking databases for compensation dispersed

Data will be stored and transported:

- All data collected through this project will be kept on password protected computers on a password protected server at the Center for Health Services and Outcomes Research, Feinberg School of Medicine, Northwestern University with access only to the Project Investigators and research study team.
- All de-identified data collected at all sites through this project will be stored at Vanderbilt University Medical Center, only accessed by Dr. Gordon, on a password protected computer, on a password protected server, or viewed via a secure VPN connection.
- Paper copies of data will be stored in locked cabinets in the research team's offices.
- Digital audio recordings will be uploaded into a computer digital file.
- Electronic transcriptions of interviews, focus groups, and usability tests.
- Outputs of qualitative or statistical data analyses.
- All hardcopies of interview, focus group, and usability testing notes and surveys will be transported from the location they take place by research team members, carrying data materials in manila folders placed in a tote bag that securely keeps papers inside.

Duration of data storage:

- The data will be stored for 7 years after the completion of the study, per NU IRB policy and per NIH policy.

Access to the stored data:

- Dr. Gordon
- Dr. Agrawal
- Research Coordinators
- Project Manager
- Data Analyst
- Statistician

Responsibility for receipt or transmission of the data:

- The Research Coordinators at each study site will be responsible for sending and receiving data, and for acknowledging receipt of data within 24 hours of receipt.
- All de-identified interview and focus group data collected at Georgetown University will be transmitted via secured, encrypted email and/or Northwestern University OneDrive to Northwestern research staff.

Describe the steps that will be taken to secure the data:

- Electronic data will be stored on NU's and GU's encrypted servers.
- Printed data will be stored in locked cabinets in the research team's offices at NU and GU.
- Only authorized personnel will have access to the data.
- Data will be transported by secure means (e.g., Northwestern University OneDrive, encrypted secure e-mail).
- Authorized personnel must log into these services with a valid university Net ID and password.
- No data will be transported by flash drives, paper, or other non-encrypted means.
- Data will be stored for 7 years per NIH policy, then destroyed.

Procedures that will be used for quality control of collected data:

- Data will be double checked, and data will be double entered to foster quality control.
- We will also search for gaps in data collected on a routine basis.
- Research staff will be trained to review patient surveys as participants submit them for completeness and request that patients fill in missing data if questions were skipped.
- Research staff will routinely review submitted checklists to ensure completeness.

REDCap (Research Electronic Data Capture) is a secure, web-based application for building and managing online data capture for research studies, e.g., for surveys and databases. Northwestern is a member of the REDCap consortium. NUBIC REDCap and Staging NUBIC REDCap are accessible from the NU network only. REDCap was developed by an informatics core at Vanderbilt University with ongoing support from NCRR & NIH grants. Licensed to NUCATS but hosted on NUCATS Servers. REDCap Consortium is composed of 832 active institutional partners from CTSA, GCRC, RCMI and other institutions in 69 countries. Currently in production use or development build-status for more than 87,000 projects with over 114,000 users spanning numerous research focus areas across the consortium. REDCap Website (From NU Network): [<https://redcap.nubic.northwestern.edu>]. REDCap is worthwhile using because: 1) Security measures outnumber those of many other services (like Survey Monkey): It requires log-in authentication and data logging, and data are secured in-house on NU Servers; 2) It is designed for medical research: it utilizes a workflow methodology for designing clinical and translational research databases; 3) Data can be exported to common data analysis packages: it exports raw data and syntax files for SAS, Stata, R, and SPSS; and 4) Cost is subsidized by the Feinberg School of Medicine.

REDCap Data Security information

Q: What type of physical security is used for the server (e.g., controlled access, secure data networks, service monitoring, environmental management, disaster recovery/business continuity, reliability and scalability)?

A: The server is physically located in the secure NUIT Research Data Center on the Chicago campus. The data center has controlled access, and the server is on secure data networks behind managed firewall. The server is also monitored for service interruption, and there are DR and backup in place in case of disasters.

Q: What type of security is provided for information transmitted/entered (e.g., details of how the data is stored/technical security of server, security of the data in transmission)?

A: All user access to the server is encrypted using standard 2048-bit SSL certificate using https protocol. Project (data entry) access is only allowed from NU networks, while public survey section is available for the entire world.

Q: How is access managed?

A: REDCap system user accounts are provisioned using NUIT's netid systems through LDAP. Project level access is managed by the REDCap support team and the project owner.

Q: What measures are taken regarding password protection (e.g., complexity/construction of passwords, frequency of forced password changes)?

A: Same as NU's netid policy, as in <http://www.it.northwestern.edu/netid/password.html>

Q: What measures are taken regarding security event monitoring (e.g., monitoring of physical security, monitoring of database and application logs, monitoring of equipment for security events)?

A: All of the security related events are reviewed by the NUBIC sysadmin team. Hosts availability is monitored 24x7 via host monitoring system.

Q: Will remote access to the network be required to participate in the project?

A: No. Only NUVPN is required from off-NU campus network.

18.0 COMPENSATION FOR RESEARCH-RELATED INJURY

No compensation is available for any research-related injury.

19.0 ECONOMIC BURDEN TO PARTICIPANTS

There are no costs to participants from participating in this research.

20. CONSENT PROCESS

Study 1: Adapting *APOL1* Testing Program Components

- Potential participants will receive information about the study via recruitment letters, fliers, emails, and listserv postings. Depending on the recruitment method (opt in or opt out), potential participants will be contacted via telephone by research staff (opt out) or potential participants will contact research staff themselves (opt in).
- When research staff speak to potential participants, staff will explain the study in greater detail, including the key elements of informed consent, to assess initial interest in participation.
- **We will obtain verbal informed consent from potential participants by phone, 1 or more days prior to focus group participation.** The Research Coordinator will verbally review the verbal consent form and emphasize: (1) the voluntary nature of study participation; (2) that participation or nonparticipation will not adversely affect their medical care; (3) that the participant can withdraw from the study at any time for any reason; (4) that no identifiable information obtained from the focus groups will be shared with their doctor, or others on the transplant team (if applicable); (5) that the risk of participation in the study is minimal, but may entail a breach of confidentiality; (6) that all identifying information will be kept confidential; (7) that no identifying information will be used in any publication or report; (8) that there is no anticipated benefit to the participant's health as a result of study participation; and (9) and that participation entails being audio-recorded. The Research Coordinator will address any questions thereafter.

Study 2: Evaluating Nephrologists' *APOL1* Counseling Knowledge, Skills, and Practice

Written informed consent will be obtained from transplant nephrologists for each of the 3 Stages in Study 2, and from other clinicians for only Stage 2 in Study 2.

- After Dr. Gordon and Dr. Agrawal (at NU) or Dr. Gilbert (at GU) introduce the study at transplant nephrology division meetings, research staff will contact potential nephrologist participants via email.
- The email will provide the URL link to the online written informed consent form via REDCap (to NU clinicians and the clinicians at other sites), or DocuSign (at GU) that will cover the key elements of informed consent (e.g., nature of participation, risks, benefits, alternatives). We will use the NU informed consent form for the clinicians at other sites. The email will emphasize: (1) the voluntary nature of study participation; (2) that nonparticipation will not adversely affect their employment; (3) that the participant can withdraw from the study at any time for any reason; (4) that no identifiable information obtained from the surveys or interviews will be shared with others; (5) that the risk of participation in the study is minimal, but may entail a breach of confidentiality; (6) that all identifying information will be kept confidential; (7) that no identifying information will be used in any publication or report; (8) that there is no anticipated benefit to the participant's health as a result of study participation; and (9) and that participation entails being audio recorded.

- We will obtain 4 sets of informed consent from each nephrologist participant. Potential participants can sign the consent form online via REDCap or DocuSign prior to the needs assessment and focus group (Stage 1); pretest/posttest surveys and counseling training program (Stage 2); and participation in the *APOL1* testing program, interviews, and surveys (Stage 3 – Control Arm and Intervention Arm). The HIPAA-compliant REDCap form securely maintains the completed PDFs in the File Repository under “PDF Survey Archive”. DocuSign is an electronic signature system that saves signed documents in an encrypted account. Files can be then downloaded as individual records or bundles in a ZIP file.
- The research staff will confirm informed consent, as NIH recommends, upon emailing participating nephrologists about partaking in the subsequent surveys, interviews, and audio-recordings in Stage 3.

Study 3: Evaluating the Effectiveness of the *APOL1* Testing Program

1. We will obtain **written informed consent** from all eligible living donor candidates (control arm and intervention arm) in person or online via REDCap (at NU) or in person or online via DocuSign (at GU) before the first step of data collection (Baseline surveys).
 - The following will take place:
 - Prior to the living donor candidate’s scheduled clinic appointment, the candidate will receive a study recruitment letter by email/mail (NU) or a study recruitment flyer in a packet of information from the transplant clinic team by email (NU/GU). The letter and flyer will state that a research staff member will call the living donor candidate about the study.
 - Research staff thereafter will call donor candidates who are scheduled for clinic and screen them for eligibility using the living donor screening script. Research staff will conduct the call via phone or Zoom, depending on the donor candidate’s comfort level and choice.
 - While still on the same phone call, for those who are eligible to participate in the study and who would like to hear about the study, research staff will ask for/confirm the donor candidate’s email address and then email the informed consent form via REDCap (NU)/DocuSign (GU) at that time. The research staff member will confirm that the donor candidate received the email and ask that they view the consent form and follow along as the research staff member reviews the form.
 - If research staff are not able to contact the donor candidate prior to the donor candidate’s clinic, research staff will screen the donor candidate and conduct the informed consent process on the day of their clinic. At NU, this will be in person. At GU, this may be virtual or in person.
2. Research staff will review the written informed consent form with eligible participants emphasizing: (1) the voluntary nature of study participation; (2) that (non)participation will not adversely affect their medical care or ability to donate, (3) that the participant can withdraw from the study at any time for any reason; (4) that the risks of participation include the risk of a breach of confidentiality and privacy, psychological risks; (5) that all identifying information will be kept confidential; (6) that no identifying information will be used in any publication or report; (7) that participants may experience a benefit to the participant’s health as a result of study participation (applicable to intervention arm); and (8) that participation entails being audio-recorded. The research staff will also review the

procedures and risks pertaining to the option of genetic testing with the **Intervention Arm**. The research staff will address any questions thereafter.

3. Eligible participants' capacity to consent will be determined through engaging in "teach back" or "show me" method, which involves asking eligible participants to describe facets of the research such as the purpose of the study, its associated risks and anticipated benefits, and the voluntary nature of, and alternatives to, study participation. This method is used to confirm whether a potential participant understands what is being explained to them. The research staff will provide clarification on points for which the potential participant expresses inadequate understanding, then will ask for further "teach-back" or clarification if the potential participant's response is not clear, to ensure comprehension.
4. When informed consent is obtained in person, two copies of consent forms will be signed, and one will be returned to participants to keep for their records. When informed consent is obtained via REDCap (NU)/DocuSign (GU), an electronic copy of the signed informed consent form will be automatically emailed by REDCap/DocuSign to the participant and an electronic copy will be saved in a password-protected research file by the research staff.
5. After obtaining consent, on the day of the participant's clinic, research staff will next conduct the Baseline survey with the participant. Following the Baseline survey, **Intervention Arm** participants will receive a link to the Gia chatbot to review.
6. Next, participants will meet with their nephrologist for pre-test counseling (in person at NU, and in person or virtually at GU).
7. For **Intervention Arm** participants:
 - Research staff will re-approach participants and ask if they agree or disagree to provide a saliva sample for *APOL1* genetic testing. The consent form includes the **option** to agree or disagree to provide a saliva sample for *APOL1* genetic testing.
 - For all NU participants, and for GU participants who signed a consent form in person, participants will be given their previously-signed informed consent form to initial at the option on the form to indicate their decision.
 - For GU participants who electronically signed their informed consent form, they will receive their consent form via DocuSign with the option to initial to indicate if they agree or disagree to provide a saliva sample for *APOL1* genetic testing.
 - Timing of saliva sample collection:
 - For GU participants who attend a virtual clinic, research staff will reiterate to the participant that the saliva sample collection will take place when the participant visits the MedStar Georgetown University Hospital in-person.
 - At NU, and at GU in-person clinics, saliva sample collection will take place in person, immediately after the participant initials their consent form (i.e., agrees to provide a saliva sample for *APOL1* genetic testing)

Across all Studies, verbal and signed written informed consent forms will be scanned and entered into the NU Feinberg School of Medicine Study Tracker. At both sites, signed consent

forms will be maintained in locked cabinets in the research staff's desks/offices or saved in the participant's electronic medical record.

Re-consent Process for Living Donor Participants in the Control Arm

During recruitment of Control Arm participants, changes were made to the Study 3 consent forms to update the HIPAA Authorization section with new information to be collected from participants' medical records. Following IRB-approval of the updated consent forms, participants who previously consented to participate in the Control Arm will be asked to re-consent using the updated consent form. The following process will be used to re-consent living donor Control Arm participants:

1. Control Arm participants will receive information about the updated consent form and a link to the updated consent form in an email.
2. Research staff will call the Control Arm participants 1-2 days after the participants receive the email and explain the changes made to the consent form, review the updated form, and ask the participant if they would like to sign the updated consent form.
3. Participants will be able to choose to have a copy of their signed informed consent form emailed to them.

Setting

The study will be conducted at 3 sites:

1. Northwestern University - recruitment and data collection
2. Georgetown University - recruitment and data collection
3. Northwestern Medicine Healthcare will also serve as a site but not for recruitment or data collection purposes.

NU will serve as the **Lead Coordinating Center** in that:

- NU is the study site that will provide the administrative, clinical, and technical expertise and leadership in the design and coordination of the multi-site collaborative research for the multi-center trial.
- The principal investigator at NU (and site PI at GU) will be responsible for all site monitoring and for the coordination of participant recruitment, screening, enrollment and retention, data and safety monitoring, data collection and analysis, adherence to the protocol-directed procedures and guidelines, and the prompt review, reporting and resolution of adverse events.

NU will also serve as the **Data Coordinating Center** in that:

- NU is responsible for the collection and storage of data collected from all sites involved in the multi-site trial.

The Community Advisory Board (CAB) is described in **Section 5.0**.

21.0 WAIVER OR ALTERATION OF CONSENT PROCESS

Not Applicable.

22.0 PROTECTED HEALTH INFORMATION (PHI AND HIPAA)

The table below illustrates which Studies will require a Partial HIPAA Waiver and HIPAA Authorization to access PHI.

	Partial HIPAA Waiver	HIPAA Authorization	Consent form requests HIPAA Authorization
Study 1	Yes	No	No
Study 2	No	No	No
Study 3	No	Yes	Yes

HIPAA Authorization

The following Protected Health Information (PHI) will be obtained from all Study 3 participants (except when specified otherwise):

- Dates of:
 - Nephrologist living donor evaluation discussions
 - Doctor's order for the *APOL1* genetic test
 - *APOL1* genetic test taken
 - *APOL1* genetic test results entered into the medical record
 - Kidney-Pancreas Committee meetings
 - Living donation
 - Medical/surgical/other rule out or withdrawal from living donation
 - Referral to genetic counselor
- Content:
 - Nephrologist discussion about *APOL1* genetic testing and donation
 - Doctor's order for the *APOL1* genetic test (including DNA source for test)
 - *APOL1* genetic test results
 - Kidney-Pancreas Committee decisions
 - Reason(s) for ruling out the donor (e.g., surgical, medical, psychosocial reasons; donor withdrawal; recipient factors)
 - Genetic counselor discussion about *APOL1* genetic testing and donation
- Clinical decision support (CDS) activations and responses (i.e., documentation that nephrologist used CDS) (**Intervention arm only**):
 - Date/time that CDS was triggered in the EHR
 - Providers who saw CDS alert
 - Response to the CDS alert

Note: The EDW may be able to obtain some of the above information e.g., date of living donation. However, the Electronic Data Warehouse (EDW) may not be able to obtain many types of data. Specifically, much of the data to be collected from the EHR will be based on the integration of genetic testing into the medical record. It is precisely this integration process that is part of the research intervention in itself. Thus, the EDW will likely not be able to access the information that is undergoing development pertaining to CDS. Therefore, research staff will need to obtain direct access to Epic for EHR data collection.

- Data will also be stored in Invitae's HIPAA-protected, SOC-2 certified, encrypted, record system. Specifically, in order to use the GIA chatbot, the Research Coordinator will create a user-specific record in GIA (for the intervention arm of study 3). The Research Coordinator will enter the participant's name, date of birth, email address, and study ID number. After creating the record in GIA, a participant-specific URL link to GIA will be generated by Invitae and then provided to the study participant to access GIA directly. These aforementioned personally identifiable data, along with the meta-data about the use of GIA (e.g., duration of time using it, specific questions asked in GIA), will be retained in Invitae's system for 7 years and deleted thereafter.

Invitae stores patient (potential living donor) information in order:

1. To identify the donor so that the research team can connect the data in Invitae's system to data the research team has elsewhere about this donor (Patient ID, DOB, Name)
2. To send invites to the donor to use the Gia chat (Donor email, phone number)
3. To personalize the Gia chat experience (addressing the user by name)
4. To send a copy of the chat script to the donor, if the donor voluntarily elects to provide their email at the end of using Gia, to receive the script.

According to Invitae, many software platforms that are used in patient care in the research and clinical settings store patient data. The Invitae-Northwestern Business Agreement is designed to protect the patients and institution in these situations.

- Genetic test results and personally identifiable information will be stored in Knight Diagnostic Laboratory's (KDL) HIPAA-compliant and protected database. Specifically, in order to submit saliva samples to KDL, the sample must be accompanied by the participant's name, date of birth, gender, self-reported ethnicity, and Medical Record Number so that KDL can have enough identifiers to report the test results back to Northwestern University and Georgetown University. The Research Coordinator will write this information into the saliva sample documentation that is mailed to KDL (for the intervention arm of study 3).
- These aforementioned personally identifiable data will be retained in KDL's database for 2 years.
- KDL will retain participants' DNA and APOL1 test results in their database indefinitely because retaining medical test results is a legally required.
- KDL destroys the saliva samples upon processing them for sequencing to generate the test report. No DNA or test results are used for external research purposes. Thus, no further research is done on the DNA and test results because no consent for further research will be provided.

KDL stores direct subject identifiers because:

- a) this is required per CLIA regulations for performing genetic testing
- b) this study is sending KDL clinical samples that our study is then using the data from for research purposes
- c) the subject identifiers enable the test results to be matched with the patient/donor's medical record at Northwestern University or Georgetown University

Partial Waiver of HIPAA Authorization

We request a **partial waiver of HIPAA authorization** to review the medical records **only** for the purpose of recruitment, and ***not*** for the purpose of data collection for **Study 1**. Individuals' contact information is essential in order to identify eligible participants and recruit them.

The partial waiver of HIPAA authorization is permissible as per section 164.512(i) of the Privacy Rule:

- The use or disclosure of information involves **no more than a minimal risk** to the privacy of individuals. This research is minimal risk because the probability and magnitude of psychological harm to participants by taking part in a focus group discussion or answering an online or paper survey about their perceptions and opinions and preferences about a chatbot and counseling program is no greater than such risk encountered in the routine medical, psychological, or educational examinations, tests, or procedures of the participant population at any hospital. The research involves no procedures for which written consent is normally required outside of the research context.
 - **The research could not practicably be conducted** without the requested waiver or alteration.
 - **The research could not practicably be conducted** without access to and use of the PHI.
 - It is not practicable for individuals to sign a written HIPAA authorization because:
 - There is no way to find out which potential participants are eligible without going to their medical records for recruitment.
- Medical chart review at NU will be conducted by the Electronic Data Warehouse (EDW) analysts to identify patients from NMH who may be eligible for recruitment.
- Medical chart review will take place at GU.
- Eligibility criteria that will be given to the EDW to identify eligible individuals include: kidney transplant recipients, living kidney donors, date of transplantation or donation, Black/African American race/ethnicity, date of birth, sex/gender, and primary language spoken. These criteria are needed for recruitment purposes (to provide to the EDW) to ensure that we foster diversity in the recruitment of the sample population.

We will randomize names in the pool of potential participants received to ensure a non-biased cross-section and minimize selection bias, thereby enhancing rigor.

23.0 QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

Feasibility of recruiting the required number of suitable participants

- Both NU and GU transplant programs serve a large number of African American LDs, and are located in cities with large African American populations (30%-IL 47%-DC).
- In 2019, the number of AA LDs who attended the transplant donor evaluation clinic visit was ~40 at NU and ~60 at GU. While the estimated participation rate based on prior research²⁵⁶ is 86%, we anticipate being able to enroll at a slightly higher rate (~90%) given community engagement and culturally competent recruitment approaches.²⁵⁷⁻²⁶⁰ Power considerations were based on assuming enrollment of 56 participants in the 10-month pre-implementation period and 240 in the post-implementation period for a total of 296. Our proposed sample size will provide 80-90% power, with a two-sided type I error rate of 0.05, to detect differences in the mean Decisional Conflict Score (DCS) between arms ranging from 5.0 to 7.7, assuming standard deviations ranging from 12 to 16.²⁴⁴ Thus, our proposed sample size will provide adequate power to detect small to medium Cohen's D effect sizes.²⁶¹
- The NU transplant program performs the entire living kidney donor candidate evaluation in person on one full day. The mornings are devoted to blood and other laboratory tests. The donor candidates have some downtime late morning and midday. Living donor candidate clinics occur three days per week in the afternoon (starting at 1:00 pm), whereby transplant nephrologists meet with donor candidates. There are potentially 4 living donor candidates evaluated in each clinic, for a possible total of 12 donor candidates evaluated per week. Thus, it is feasible for 1-2 research coordinators to approach, in person, all 4 candidates in a given day, to assess interest in study participation and obtain informed consent.
- The GU transplant program performs the living kidney donor candidate evaluation in a span of a couple days. The first portion is done virtually over Zoom. During this time, the donor candidate meets with the transplant team, which includes meeting with the transplant nephrologist. There are potentially 6 living donor candidates evaluated in each clinic. There are two living donor clinics each week, for a possible 12 donor candidates evaluated per week. After the virtual clinic, the donor candidates are scheduled to come in-person to GU for clinical exams.

Qualifications of Research Team

Northwestern University:

- The multidisciplinary research team is well qualified given their expertise in *APOL1*, living donation and transplantation, genetics, disparities, clinical trials, implementation science, bioethics, and community engagement.
- **It is important to note that two genetic counselors helped with the study design and the consent process.**
- Akansha Agrawal, MBBS, is a transplant nephrologist and clinically evaluates LDs; she will champion, adapt, and deliver the *APOL1* testing program into clinical practice.
- NU Co-Investigators include:
- Catherine A. Wicklund, MS, CGC is Associate Professor in the Center for Genetic Medicine, Director of the Graduate Program in Genetic Counseling, a genetic counselor, and will serve as a content expert in genomics and EHR integration.

- Debra Duquette, MS is Associate Professor of Medicine, a genetic counselor, and will provide expertise in genomics education to adapt and deliver the genomic training to nephrologists.
- Darius Tandon, PhD is Co-Director of the Center for Community Health and will bring expertise in stakeholder engagement in translational research.
- Lutfiyya Muhammad, PhD is Assistant Professor of Preventive Medicine, Division of Biostatistics, and will bring expertise in biostatistics to oversee data management and statistical analysis plan.

NIH Grant Principal Investigator, at Vanderbilt University Medical Center:

- Elisa J. Gordon, PhD, MPH is Professor of Surgery, and a medical anthropologist and clinical ethicist. She has experience leading multi-site clinical trials, and will lead the proposed study.

Co-Investigator at University of Utah:

- Justin D. Smith, PhD is Associate Professor is an implementation science expert and will provide expertise in implementation science methods and analysis.

Georgetown University:

- GU Site PI, Alexander Gilbert, MD is a transplant nephrologist, clinically evaluates LDs, and will oversee, champion, and deliver the *APOL1* testing program into clinical practice.
- GU Co-Investigator, Matthew Cooper, MD is Director of Kidney and Pancreas Transplantation at GU, a transplant surgeon, clinically evaluates LDs, and will help champion the *APOL1* testing program into clinical practice.
- GU Transplant nephrologists will be engaged in the Study 2: Nephrologist Study and Study 3 control and interventional arms.

Community Advisory Board Members:

The Community Advisory Board (CAB) is comprised of patient and community stakeholders who bring kidney disease, transplantation, donation, and African American religious, civic, and community perspectives to help adapt the genetic testing program. CAB members have helped with editing the consent forms and study design. CAB Members include:

1. Jackie Burgess-Bishop, CEO, National Kidney Foundation of Illinois
2. Monica Fox, Director of Community Engagement, National Kidney Foundation of Illinois
3. Ms. Marion L. Shuck, MA, MPhil, Director, Donor Family Services & Community Outreach, Gift of Hope Organ Procurement Organization
4. Mr. George Wells, Live kidney donor
5. Dr. Phalese Binion, Westside Ministers Coalition
6. Ms. Joann Howard-Burden, Kidney transplant recipient (from living donor)
7. Ms. Vea Crawford, Prior Chair of the Health Committee of the NAACP National Board
8. Kareem Butler, Director of Learning & Evaluation, Research and Policy Center, The Chicago Urban League

External Consultants:

- Mona Doshi, MD is a transplant nephrologist at University of Michigan, a site PI for the APOLLO study, and will provide expertise on *APOL1* in LDs.
- Charmaine Royal, PhD is Associate Professor of African and African American Studies at Duke University, and will provide expertise in the intersection of racial identity and genomics.

- Richard Sharp, PhD is Professor and Chair of Biomedical Ethics at Mayo Clinic, and will provide content expertise in bioethical issues in genomics.

American Association of Kidney Patients (AAKP)

Team Training

- Dr. Gordon is committing 25% effort to this study, all years of the study, to complete this study.
- Full time research staff are also committed to the conduct of this study.
- Dr. Gordon will provide a comprehensive training program for all research staff at NU and GU over the course of 4 weeks, early in the study, which entails:
 - Self-driven:
 - completion of CITI training
 - completion of GCP training
 - reading NIDDK website about kidney disease and kidney transplantation
 - reading 5-10 clinical and ethics articles about *APOL1*
 - reading the grant application
 - reading the IRB protocol
 - reading the Manual of Operations (MOP)
 - reading 1 article about community engagement
 - reading 5 articles about conducting surveys, focus groups, and interviews
 - reading 5 articles about conducting qualitative data analysis
 - Dr. Gordon-led:
 - Reviewing the organizational chart and collaborating organizations
 - reviewing research staff's job roles and responsibilities
 - reviewing expectations for research staff's team engagement and participation in routine meetings, commitment to the study, and opportunity to contribute ideas about improving study efficiencies
 - reviewing study aims, hypotheses, and desired outcomes
 - reviewing data collection: data collection materials (surveys, interviews, checklists, medical record review forms), the MOP, draft databases for surveys, the recruitment and informed consent processes, the data entry processes, participant compensation processes
 - reviewing study procedures: preparing staff for conducting surveys, interviews, focus groups, checklists,
 - reviewing genetic testing procedures: preparing staff for saliva collection and shipping, and documentation
 - reviewing the role of the CAB, and how community engagement is part of the study
 - reviewing the timeline and milestones
- A Transplant Psychologist (Dr. John Franklin) is available in case study participants need assistance as a result of research participation.

24.0 MULTI-SITE RESEARCH

- NU will serve as the single IRB of record for GU and VUMC (see letters from Nathalia Henry 2-14-20 and 4-17-20).
- All recruitment methods, study procedures, data collection activities are the same at NU and GU.
- A Data Use Agreement has already been established between NU and GU.
- A Data Sharing Agreement has been set up between NU and VUMC.
- We will use the SMART IRB as our reliance pathway.
- No data will be shared with VUMC until after the reliance agreements are fully executed that include VUMC.

We will use several processes to ensure communication among sites:

- All sites will have the most current version of the study protocol, consent documents, and HIPAA authorization. NU will provide GU and VUMC with all of the aforementioned NU IRB approved study documents so that GU and VUMC can adapt them to the their institutional settings.
- All required approvals (initial, continuing review and modifications) will be obtained at each site (including approval by the site's IRB of record) prior to initiating recruitment and data collection activities.
- All modifications will be communicated to sites and approved (including approval by the site's IRB of record) before the modification is implemented.
- All sites will safeguard data, including secure transmission of data, as required by local information security policies.
- All local site investigators will conduct the study in accordance with applicable federal regulations and local laws.
- All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.
- GU and VUMC will notify NU about any Reportable New Information (RNI) or adverse events or serious adverse events within 24 hours of becoming aware of them.
- NU will notify GU and VUMC about any RNIs within 3 days of submitting the RNI report to the NU IRB so that GU and VUMC can similarly implement safeguards to prevent similar RNIs from occurring at GU and VUMC.
- Dr. Gordon will lead weekly meetings with both research teams at both study sites, during which time any concerns will be discussed. All members of the research team will have Dr. Gordon's personal cell phone number [708-646-7973] and email addresses [e-gordon@northwestern.edu and elisa.gordon@vumc.org] to contact her at any time about the study.

- NU and GU will enter data into REDCap, as hosted by NU, thus, NU will have access to all data collected. Data will be entered into REDCap within 24 hours of data collection.
- NU research team will prepare a Manual of Procedures (MOP) and share the MOP with the GU research team to ensure that recruitment, data collection, data entry and management is conducted systematically and consistently across study sites.

Study 1

Both NU and GU will be involved in recruiting potential participants, obtaining informed consent, conducting focus groups, data entry, and qualitative data analysis.

Study 2

Both NU and GU will be involved in recruiting potential participants, obtaining informed consent, participating in a focus group, participating in the counseling training program, conducting pretest/posttest surveys, conducting longitudinal surveys, audio-recording nephrologists' delivery of counseling, and data entry. Northwestern University will analyze the data.

Study 3

Both NU and GU will be involved in recruiting and screening potential LD participants, obtaining informed consent, conducting surveys, providing the chatbot link, collecting and shipping saliva samples, performing direct audio-recordings of the LD-nephrologists post-test counseling discussions, developing the *APOL1* policy, *APOL1* test result integration into the EHR, and data entry. Northwestern University will conduct all statistical analyses as the data coordinating center.

Dr. Gordon at VUMC will conduct telephone surveys with NU nephrologist study participants in Study 3. No human subjects will be recruited at VUMC. VUMC will be involved in data analysis.

Multi-Site Communications

We will perform the following steps through holding routine research team meetings, and all changes to protocols will be communicated in a timely manner:

- NU created a OneDrive folder accessible to all study sites.
- OneDrive will host all NU-prepared IRB materials (e.g., protocol, recruitment letters, consents) for GU and VUMC to use and tailor to their own IRB's requirements.
- All required approvals will be obtained at GU and VUMC (including approval by the site's IRB of record).
- All anticipated or proposed IRB modifications will be communicated by NU to coordinate efforts with GU and VUMC, as needed.
- All submitted IRB modifications must be approved by the study site's IRB of record before the study site may implement the modification.
- All problems with regard to adverse events, and study protocol breaches will be communicated by the GU and VUMC study site PI to Dr. Gordon and Dr. Agrawal within 24 hours of problem identification.
- All other problems including staff turn-over or institutional changes in policy and practices relevant to data collection, as well as interim results and the closure of a study will be communicated to Dr. Gordon and Dr. Agrawal within 48 hours.
- NU and Dr. Gordon will coordinate and schedule routine research staff and study team meetings to discuss study progress, interim results, and troubleshoot any problems.

For the secondary analysis of the CFIR interview transcripts with transplant nephrologists, the University of Utah IRB Reliance contact and the Northwestern IRB Reliance contact both agreed on February 7, 2024 that such analysis does not comprise human subjects research, and that a Data Sharing Agreement is not required and that the University of Utah does not need to be added as a study site for oversight by the Northwestern single IRB. However, both sites agreed that of the performance of this analysis by the University of Utah co-investigator (Dr. JD Smith and his Fellow, Dr. James Merle) and the current research team (e.g., Dr. Gordon at VUMC) should be documented in the IRB protocol. This note comprises such documentation.

Data Sharing

A Data Use Agreement (DUA) was established on 8/6/21 between Northwestern University and Georgetown University (GU), to document the data being shared by Georgetown University with Northwestern University and the terms and conditions with respect to issues such as data ownership, permitted use of data, publication of results, disposal of the data, and liability. De-identified data (focus group, aggregated demographic data, survey data, and tracking databases to document participation rates) from the Georgetown University collaborating research team (Drs. Gilbert and Cooper, site-PIs) will be shared with Northwestern University, as the data coordinating center, to foster comprehensive qualitative and quantitative analysis and enable comparison between study sites in participants' perspectives about decision making, informed consent process, and the *APOL1* genetic testing program. The consent forms at GU include a statement regarding data sharing, and that Northwestern may inspect/receive the data because NU is the site coordinating the data. The DUA between NU and GU will be revised to incorporate VUMC. The revised DUA will entail GU sending data to NU and VUMC, and will entail NU sending all data to VUMC. The data shared with VUMC will be deidentified except for dates that will be included.

Future IRB Modifications

We plan to submit the following modifications for IRB review and approval prior to initiating data collection activities pertaining to these revised steps. Documents that will be refined or developed for these modifications will be uploaded to the Supporting Documents section of the eIRB.

- **Focus Group Moderator's Guide (Study 1) – Submitted in IRB Modification and Approved**
 - After developing the initial draft of Chatbot content and design, we will modify the Moderator's Guide and submit for review
 - After conducting each wave of focus groups [each wave consists of ~ 3 focus groups], we will submit a refined Moderator's Guide.
- **Chatbot content and design (Study 1) – Submitted in IRB Modification and Approved**
 - Before conducting the first Focus Group, we will submit an initial draft of Chatbot content and design
 - After completing each of the 3 waves of Focus Groups, we will submit refined Chatbot content and design for IRB review
- **Nephrologist Counseling Training Program (Study 2) – Submitted in IRB Modification and Approved**

After completing the Needs Assessment and Nephrologist Focus Group, we will submit the Nephrologist Counseling Training Program content, format, and duration

- ***APOL1* Policy (Study 3)**
After writing the formal *APOL1* policy, we will submit it
- ***APOL1* Brochure (Study 3) – Submitted in IRB Modification and Approved**
After updating the brochure, we will submit the revised version.
- **Electronic Health Record (EHR) Clinical Decision Support (Study 3)**
After writing the clinical decision support content for *APOL1* test results, we will submit it
- **Single IRB agreements between Northwestern University and Georgetown University and between Northwestern and Vanderbilt University Medical Center**
Initial agreements and IRB modifications will be submitted at each site, as required.

24.0 SOURCES OF FUNDING

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- NIH/NIDDK 5 year R01