Implementation of a culturally competent APOL1 genetic testing programme into living donor evaluation: A two-site, non-randomised, pre–post trial design

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ABSTRACT

Introduction While living donor (LD) kidney transplantation is the optimal treatment for patients with kidney failure, LDs assume a higher risk of future kidney failure themselves. LDs of African ancestry have an even greater risk of kidney failure post-donation than White LDs. Because evidence suggests that Apolipoprotein L1 (APOL1) risk variants contribute to this greater risk, transplant nephrologists are increasingly using APOL1 genetic testing to evaluate LD candidates of African ancestry. However, nephrologists do not consistently perform genetic counselling with LD candidates about APOL1 due to a lack of knowledge and skill in counselling. Without proper counselling, APOL1 testing will magnify LD candidates’ decisional conflict about donating, jeopardising their informed consent. Given cultural concerns about genetic testing among people of African ancestry, protecting LD candidates’ safety is essential to improve informed decisions about donating. Clinical 'chatbots', mobile apps that provide genetic information to patients, can improve informed treatment decisions. No chatbot on APOL1 is available and no nephrologist training programmes are available to provide culturally competent counselling to LDs about APOL1. Given the shortage of genetic counsellors, increasing nephrologists’ genetic literacy is critical to integrating genetic testing into practice.

Methods and analysis Using a non-randomised, pre–post trial design in two transplant centres (Chicago, IL, and Washington, DC), we will evaluate the effectiveness of culturally competent APOL1 testing, chatbot and counselling on LD candidates’ decisional conflict about donating, preparedness for decision-making, willingness to donate and satisfaction with informed consent and longitudinally evaluate the implementation of this intervention into clinical practice using the Reach, Effectiveness, Adoption, Implementation and Maintenance framework.

Ethics and dissemination This study will create a model for APOL1 testing of LDs of African ancestry, which can be implemented nationally via implementation science approaches. APOL1 will serve as a model for integrating culturally competent genetic testing into transplant and other practices to improve informed consent. This study involves human participants and was approved by Northwestern University IRB (STU00214038). Participants gave informed consent to participate in the study before taking part.


BACKGROUND

Living donor (LD) kidney transplantation is the optimal treatment for patients with...
kidney failure,\textsuperscript{1, 2} with greater patient and graft survival and quality of life than deceased donor transplantation\textsuperscript{3, 4} or dialysis.\textsuperscript{5, 6} Patients of African ancestry have disproportionately greater rates of chronic kidney disease (CKD) and kidney failure compared with White patients. They also comprise disproportionately greater representation on the transplant waitlist but receive fewer transplants than White patients.\textsuperscript{7, 8} The estimated risk of kidney failure at 15 years post-donation is higher in LDs of African ancestry than in White LDs: 74.7 versus 22.7 per 10,000 LDs.\textsuperscript{9, 10} These findings have intensified the transplant field’s concerns with protecting LD safety, improving LD informed consent and reducing LD disparities in post-donation kidney disease.\textsuperscript{11-13} LD, clinician and health system factors contribute to this disparity for LDs,\textsuperscript{14, 15} along with systemic racism and social determinants of health. In addition, the higher prevalence of CKD among patients of African ancestry compared with White patients has been attributed to \textit{Apolipoprotein L1} or ‘\textit{APOL1}’ risk variants,\textsuperscript{16} which are found predominantly in individuals of African ancestry.\textsuperscript{16-18} Among patients of African ancestry \textit{without} CKD, 13\%–15\% have two \textit{APOL1} risk variants, and 39\% have one risk variant.\textsuperscript{10, 19} Having two \textit{APOL1} risk variants is associated with a 10-fold greater odds of focal segmental glomerulosclerosis-attributed kidney failure.\textsuperscript{16} More than 3 million individuals of African ancestry in the USA are estimated to have two risk variants.\textsuperscript{20} Kidneys from deceased donors with two \textit{APOL1} risk variants had significantly greater risk of graft failure (two-fold HR) in recipients than kidneys from deceased donors with \textless 1 variant.\textsuperscript{21, 22} Young male LDs of African ancestry with two \textit{APOL1} risk variants were at highest risk of CKD post-donation compared with female and European American LDs.\textsuperscript{23}

**The research-to-practice gap**

The 2017 KDIGO Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors advises ‘…considering \textit{APOL1} genotyping in LD candidates with sub-Saharan African ancestors’,\textsuperscript{24, 25} given that \textit{APOL1} risk variants evolved in this region. The American Society of Transplantation in 2015 reported that current data were insufficient to support testing all LD candidates of African ancestry due to the lack of long-term population-level data on \textit{APOL1} risk variants\textsuperscript{25} and the lack of \textit{APOL1}’s specificity in predicting disease.\textsuperscript{26, 27} \textit{APOL1} testing is controversial because of the lack of definitive evidence on the causal link between \textit{APOL1} risk variants and LDs’ health outcomes, and the consequent ethical dilemmas raised, as described below. Thus, some physicians are waiting for results from the NIH-funded APOLLO study before implementing \textit{APOL1} testing into their clinical practice.\textsuperscript{28} Others posit that LDs of African ancestry should be screened for \textit{APOL1} variants to risk stratify LDs; the presence of two risk variants should comprise a relative contraindication to donation requiring careful counseling and consent of LDs.\textsuperscript{12, 26, 28, 29} \textit{APOL1} testing of LDs raises the ethical dilemma of whether to permit LDs of African ancestry with two \textit{APOL1} risk variants to donate.\textsuperscript{29, 30} Donating could place such LDs at even greater harm, thereby challenging: (a) the ethical principle of non-maleficence as LDs gain no direct medical benefit from donation\textsuperscript{31-33} and (b) the ethical justification for living donation: when ‘benefits to both the donor and the recipient outweigh the risks associated with the donation and transplantation’.\textsuperscript{33} Not allowing LDs of African ancestry with two risk variants to donate could protect their safety by reducing their risk of CKD, but not donating could exacerbate disparities in access to LD transplantation for candidates of African ancestry and reduce patient survival.\textsuperscript{26, 34}

Genetic counselling and shared decision making (SDM) about undergoing \textit{APOL1} genetic testing and living donation with \textit{APOL1} risk variants are especially warranted given that donating is a preference-sensitive decision and \textit{APOL1} poses elevated risks for LDs.\textsuperscript{35} Transplant physicians are increasingly adopting \textit{APOL1} testing,\textsuperscript{36-38} but they do not consistently inform LD candidates about \textit{APOL1} genetic testing, perform genetic counselling or practice SDM with LDs.\textsuperscript{36-39} This variation results partly from physicians’ lack of practical knowledge and skills in \textit{APOL1} counselling, and fear that \textit{APOL1} testing will deter LDs from donating, which would further exacerbate African American transplant candidates’ disparities in access to LD kidney transplantation.\textsuperscript{30, 36}

Genetic counselling is ‘the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease’.\textsuperscript{40} Counselling involves education about inheritance, testing and prevention to promote informed choices and includes SDM.\textsuperscript{40} Counselling is effective in reducing decisional conflict, increasing knowledge and improving accuracy of risk perception,\textsuperscript{41} which improve informed consent. Importantly, while LDs are usually eager to donate to improve family or friends’ health, many are uncertain about donating.\textsuperscript{42-44} Concerns about long-term health conditions after donation were a reason for LDs’ reluctance to donate among 34\% of potential donors (n=53) participating in in-depth interviews in a study in the Netherlands\textsuperscript{42} and among 40\% of LDs (n=174) in a retrospective US survey study.\textsuperscript{45} Although most (87\%) LDs of African ancestry in an interview study (n=23) expressed willingness to undergo \textit{APOL1} testing, fewer (61\%) would have donated if they had two risk variants.\textsuperscript{47} In addition, most interviewed LDs of African ancestry (81\%) ‘strongly agreed’ or ‘agreed’ that \textit{APOL1} test results would have helped them decide whether to donate.\textsuperscript{47} Most LDs of African ancestry (82\%) in a focus group study (n=17) also would have wanted to receive genetic counselling about \textit{APOL1} testing during LD evaluation.\textsuperscript{43} Thus, \textit{APOL1} risks may magnify LDs’ decisional conflict about donating,\textsuperscript{47} which, as a prospective survey study of potential donors (n=53) in Taiwan found, is significantly associated with LDs’ lower likelihood to actually donate.\textsuperscript{43} However, no studies have trained transplant
physicians on APOL1 genetics, counselling and race and prospectively assessed the impact of APOL1 testing and counselling on LDs’ donation decisions.

Barriers to the clinical integration of genomic testing include: providers’ lack knowledge and preparedness to provide genetic services; healthcare systems do not enable electronic health records (EHRs) to make readily accessible genetic test results and clinical practice guidelines advise APOL1 testing LDs of African ancestry but do not specify how to ascertain ancestry.

‘Race’-based care or ‘racialised medicine’ conflates the outdated social construction of ‘race’ as biological domains of influence, including: limited access to insurance coverage for transplantation, providers’ poor-quality communication about and limited referral to transplantation, and transplant allocation policies. Such systemic barriers have contributed to disproportionately lower rates of organ transplantation among African American patients and other minoritised patients.

Genetic testing is one factor that can potentially contribute to systemic racism in transplantation and in other clinical contexts. Genetic testing can potentially exacerbate or mitigate systemic racism. On one hand, genetic testing can magnify systemic racism if it is not offered in an equitable way to all patients. At the individual level, many individuals of African ancestry hold cultural concerns about genetic testing (eg, beliefs and concerns about misuse of testing, mistrust in the medical system) and fear that APOL1 test results would lead to psychological distress, stigmatisation of the community of African ancestry and health insurance discrimination. On the other hand, preparing the transplant provider workforce to offer APOL1 genetic testing to all LDs of African ancestry and to provide genetic counselling in a culturally appropriate manner can help to reduce inequities by eliminating provider bias, acknowledging historical distrust of institutions and fostering trust. Culturally competent care can increase knowledge among people of African ancestry about donation and LD rates.

Study aims

Aim 1. Adapt Gia and transplant counselling to APOL1 for use in routine clinical practice. We will adapt a chatbot, Gia® (Genetic Information Assistant), and nephrologist counselling to ensure that they are culturally targeted and competent, by engaging communities of African ancestry and experts in genetics, transplantation and bioethics. The goal of the adaptation process is to ensure implementation of the genetic testing and counselling components on a broad scale with minimal disruption to provider workflow.

Aim 2. Evaluate the effectiveness of this intervention on decisional conflict, preparedness and willingness to donate in a two-site, non-randomised, pre–post trial design. We hypothesise the intervention will: decrease LDs’ decisional conflict about donation. 

H 2: increase LDs’ preparedness for decision-making about donation.

H 3: not decrease LDs’ willingness to donate.

Aim 3. Evaluate the implementation of this intervention into clinical practice by using the RE-AIM framework to longitudinally evaluate nephrologist counselling practices and LDs’ satisfaction with informed consent.

We will use the Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) framework to longitudinally evaluate implementation outcomes (ie, acceptability, appropriateness, feasibility, reach, adoption and fidelity). We hypothesise implementation will:

H 4: increase nephrologists’ knowledge and skill in delivering counselling for APOL1 testing and donation.

H 5: increase LDs’ satisfaction with informed consent about donation.

METHODS

Overview and rationale for the study design

Because genetic testing and chatbots are effective interventions, scientific focus can be shifted towards the implementation of genetic testing and the chatbot for APOL1 and LDs of African ancestry. The non-randomised clinical trial, with a pre–post implementation evaluation, uses a type II effectiveness–implementation hybrid approach to simultaneously and rigorously test a prospective implementation strategy during an effectiveness trial to facilitate translation into clinical practice. Accordingly, control arm participants will be recruited during the preimplementation period, and intervention arm participants will be recruited during the postimplementation period.

Study sites

The proposed study will be conducted at Northwestern University (Chicago, IL) and Georgetown University (Washington, DC). Both transplant programmes have a large number of Black/African American LDs and are in cities with large populations of Black/African American people (30%-Chicago, 47%-DC). Neither site systematically identifies the African ancestry of LDs or has a policy on LD selection for APOL1 testing. Neither site uses SDM to aid in donation decisions.

APOL1 genetic testing and counselling programmes

APOL1 genetic testing

1. Asking all LD candidates about their ancestry: asking all LDs about their ancestry will include LDs with
Table 1  APOL1 counselling training programme content domains

<table>
<thead>
<tr>
<th>Module</th>
<th>Description: after completing the training, nephrologists will be able to...</th>
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<tbody>
<tr>
<td>Introduction</td>
<td>Articulate the programme’s purpose and who it is designed to help</td>
</tr>
<tr>
<td>APOL1 and kidney disease</td>
<td>Define APOL1 and its relationship to kidney disease</td>
</tr>
<tr>
<td>APOL1: risks, benefits and limitations of living kidney donation and genetic testing to living donors, their family and their recipients</td>
<td>Describe the risks of having two risk variants on LDs’ post-donation health, their reproduction and on other family members; communicate about genetic risks as modifiable vs non-modifiable</td>
</tr>
<tr>
<td>Genetic variation and ‘Race’: knowledge and practice</td>
<td>Communicate about APOL1 and address the values and beliefs among people of African ancestry about genetic testing in a culturally and socially sound manner</td>
</tr>
<tr>
<td>Access, insurance, privacy, and confidentiality of testing and test results</td>
<td>Explain how LDs’ privacy and confidentiality of test results will be protected; the limits of the Genetic Information Nondiscrimination Act of 2008; what will happen to test results, and who has access to them</td>
</tr>
<tr>
<td>Ethics</td>
<td>Compare ethical implications of donating and not donating</td>
</tr>
<tr>
<td>Shared decision-making</td>
<td>Engage in SDM with LD candidates with two risk variants about donating; explain the relative benefit to recipients of LDKT vs staying on dialysis</td>
</tr>
<tr>
<td>Case study discussion</td>
<td>Apply concepts learnt in modules to an actual case.</td>
</tr>
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</table>

APOL1, Apolipoprotein L1; LD, living donor; LDKT, Living Donor Kidney Transplantation; SDM, shared decision-making.

African ancestry who might otherwise be missed.48 This approach coincides with a pan-ethnic genetic screening paradigm72 and avoids reinforcing the phenotype-based construct of ‘race’ for selecting LDs for APOL1 testing.

2. Offering APOL1 testing to all LD candidates with African ancestry that pass initial screening; half of LD candidates do not pass.73 Testing LDs early avoids unnecessary expense of other tests for LDs who will be ruled out.47 74 APOL1 genotyping all LD candidates of African ancestry is cost-effective in preventing CKD.75

**APOL1 genetic counselling**

1. A clinical chatbot will provide pre-APOL1 genetic testing information based on LDs’ information needs.75 Chatbots increase informed treatment decisions and reduce decisional conflict.76 77 This study will create the first chatbot on APOL1.

2. Nephrologists will provide post-APOL1 counselling about test results to normalise APOL1 in the routine LD evaluation process (table 1). Nephrologists will engage in SDM with LDs who test positive for two risk variants about donating, as recommended.78

3. A culturally competent educational brochure on APOL1 that our team previously developed will be given by nephrologists to LD candidates of African ancestry during evaluation and be available in the transplant centre waiting room.48

**Implementation strategies**

We will use several implementation strategies to accomplish the study’s aims,79 multiple methods to document them81 82 (figure 1) to specify the conceptual associations between determinants, strategies and the hypothesised/observed mechanisms and outcomes that result. The Implementation Research Logic Model (IRLM) provides a comprehensive set of strategies to be used. The following strategies are the primary focus of the study: establishing academic–community partnership, leveraging a Community Advisory Board (CAB), engaging patients, using a chatbot, educating and training transplant nephrologists, integration of genetic testing into the EHR and financing APOL1 testing. Additional details on each of the primary strategies are available in online supplemental file 1 and online supplemental file 2.

**Patient and public involvement**

We established a CAB comprised of transplant patients and community leaders who provided input on the study design, outcome measures, informed consent and recruitment and retention procedures. The CAB will review study results to provide insights into interpretation and foster dissemination.

**Assessment strategy, measures and data analysis**

**APOL1 intervention**

The APOL1 testing programme has been designed to fit within the routine LD evaluation process of the two sites, which limits LD clinic visits to 1 day. LDs will have four touchpoints of data collection (table 2). Between the labs (eg, blood, EKG, CT) and nephrology visit, research staff will screen all LDs by asking the 3 ancestry screening questions, obtain informed consent for study participation, conduct baseline surveys and provide the chatbot link to use for 5–7 min (T1). Tablets will be provided if LDs do not have a smartphone. The three ancestry questions include: ‘What ethnic/racial groups do you identify with?’ (eligible for study: Black, African American, Jamaican, Barbadian, Grenadian, Brazilian from Salvador, Trinidadian, Panamanian, Honduran, Haitian, Garifunan, Palenque, Guyanan, Dominican, Peruvian, Belizean and
Native American); ‘Are you aware of any biologically-related family with African ancestry?’ and ‘What is your ancestry?’ After LDs meet with the nephrologist, staff will ask for informed consent for APOL1 testing, collect a saliva sample and mail it to the laboratory. Research staff call LDs a week later to qualitatively assess LDs’ perceptions of the chatbot, and its impact on outcome measures (T2). Clinical decision support in the EHR will alert the nephrologists when APOL1 test results return and will prompt the nephrologists to call LDs to discuss the APOL1 test results and engage in SDM about donation. Research staff will call LDs 1–2 business days thereafter to qualitatively assess LDs’ perceptions of the counseling and its impact on outcome measures (T3). Research staff will call LDs 1 month after donating/rule out for donation (eg, medical, surgical, psychological) to assess decisional regret (T4). During year 1, which serves as the preimplementation control phase, both sites will only assess T1 and T4 LD outcomes.

Statistical analyses

Descriptive summaries will be generated for all data (eg, means and SD, medians, IQR and ranges for continuous data; counts and frequencies for categorical data). Graphical summaries (ie, 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 enrolment periods within each centre.

Analyses for H1 will employ a linear mixed effect model with fixed effects for arm (pre or postimplementation) and study period. The included random centre effect will allow for separation of within-centre and between-centre variance estimates. Specifically, we will estimate a CI for the difference in medians to compare the willingness to donate between the preimplementation and implementation periods. If the lower limit of a two-sided 95% CI is within the margin of non-inferiority, we will have evidence that the APOL1 counselling 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. Youn (age 35–44 years), male, LDs of African ancestry with APOL1 risk variants have the highest risk of developing CKD, although most LDs are women.23 85
Thus, planned subgroup analyses will consider assessment of LD outcomes by sex and age groups. These analyses will be deemed exploratory given power considerations.

Implementation of the APOL1 testing programme into clinical practice

Assessment of determinants is focused on the inner and outer context variables of the Consolidated Framework for Implementation Research (CFIR). Implementation evaluation follows the RE-AIM evaluation framework (table 3). We will also test changes in knowledge and self-efficacy for genetic counselling among nephrologists as a hypothesised mechanism affecting their decision to adopt the APOL1 counselling component of the intervention.

Determinants

We will conduct in-depth interviews with nephrologists about their perceived facilitators, barriers, organisational capacity and adaptations to the APOL1 testing programme using the CFIR interview guide (www.cfirguide.org). Nephrologists will be interviewed before implementation, after implementation and before the implementation period ends. Interviews will be conducted in person or by phone by an experienced interviewer, last 30–45 min, and be audio-recorded.

Acceptability, appropriateness, and feasibility

We will conduct brief phone surveys to assess LDs’ and nephrologists’ perceptions of the APOL1 testing and counselling programme using validated surveys and standard methods with LDs at T3 and T4. Nephrologists are surveyed after completing training but before enrolling LDs, after administering the APOL1 intervention for 2 months and after 1 year.

Reach and adoption

We will calculate Reach using study enrolment data using continuous 3-month sampling periods to closely approximate LDs counselled at any given point. We will use nonlinear growth modelling approaches to examine rate of change in reach over time. Reach is also the proportion of LDs who consent and give saliva samples out of LDs offered APOL1 testing. We expect to achieve an 80%

### Table 2 Intervention measures collected across time (T)

<table>
<thead>
<tr>
<th>Independent measures</th>
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<tbody>
<tr>
<td>Sociodemographics including age, gender, marital status, education, income level, self-identified racial and ethnic identities, and one validated health literacy item.</td>
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<tr>
<td>Relationship between LD and recipient: directed (spouse, parent, adult child, sibling, friend, etc.) vs non-directed donor.</td>
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<tr>
<td>Smartphone ownership and use: will be assessed by two yes/no questions for example, ‘Do you already have a working “smartphone”-capable cellular device (Internet capable)’?</td>
</tr>
<tr>
<td>Knowledge of genetics will be assessed by nine true/false items from validated surveys.</td>
</tr>
<tr>
<td>Self-efficacy with genetic information will measure LDs’ confidence and ability to understand and use genetic information in a 5-item Likert scale.</td>
</tr>
<tr>
<td>Decision to undergo APOL1 genetic testing will be measured in two items: ‘Do you plan to get the APOL1 test’ or ‘Did you decide to get the APOL1 test?’ (yes/no)</td>
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<thead>
<tr>
<th>Outcome measures</th>
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<tbody>
<tr>
<td>Decisional Conflict Scale (DCS) will measure perceived uncertainty in decision-making about donating and satisfaction with effective decision-making, and nephrologists’ decision-making before and after genetic counselling. The revised DCS includes 16 items organised into a Total score and Uncertainty, Informed, Values Clarity, Support and Effective Decision subscores measured on a 5-point Likert scale. Test–retest reliability coefficient=0.81. Internal consistency coefficients=0.78–0.92. Cronbach’s α ranged from 0.92 to 0.96.</td>
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<tr>
<td>Preparation for Decision Making Scale (PDMS) is a process measure that will assess LDs’ perception of how useful the chatbot and counselling is in preparing them to communicate with their physician and make the donation decision. PDMS includes 10 items measured on a 5-point scale. Cronbach’s α ranged from 0.92 to 0.96.</td>
</tr>
<tr>
<td>Willingness to Donate will be measured in one 10-point Likert item, as used elsewhere.</td>
</tr>
<tr>
<td>Decision Chosen will be assessed via EHR review as donated/not donated.</td>
</tr>
<tr>
<td>Perceptions of Culturally Competent Counseling will be assessed by 10 Likert items.</td>
</tr>
<tr>
<td>Shared Decision Making (SDM-Q9) will assess SDM in nine items. Cronbach’s α=0.93.</td>
</tr>
<tr>
<td>Satisfaction with the Informed Consent Process will be measured using 20 validated closed-ended questions that assess decision-making quality, decision satisfaction and perception of information. It takes 4 min to complete.</td>
</tr>
<tr>
<td>Decision Regret Scale (DRS) will assess LDs’ level of regret with (not) donating, and with (not) undergoing APOL1 testing. DRS consists of 5 items, Cronbach’s α=0.81–0.92.</td>
</tr>
</tbody>
</table>

APOL1, Apolipoprotein L1; EHR, electronic health record; LD, living donor.
reach rate at the centre level. We will determine the representativeness of participants by comparing demographic characteristics between participants and non-participants. Adoption is the number and proportion of nephrologists who deliver genetic counselling to ≥1 enrolled participant. We will assess whether nephrologists vary in offering counselling based on LD and nephrologist factors using analysis of covariance (ANCOVA) and multiple regression. Reach and adoption rates will be compared across centres using analysis of variance (ANOVA) and within-nephrologist using multilevel modelling techniques.

Fidelity
The extent to which the APOL1 testing programme is delivered as intended will be assessed by: (1) nephrologist adherence to prescribed counselling behaviours and (2) adherence to the chatbot strategy. Because counselling occurs by telephone, research staff will be present to audio-record discussions, and thereafter listen to a random sample (50%) of sessions (in the control and intervention arms) using a standardised observer checklist to document and evaluate the observed delivery and quality of prescribed counselling behaviours to generate a fidelity score. We will compare fidelity across nephrologists (ANCOVA), across centres (ANOVA) and across time to test for drift (non-linear mixed model with time by nephrologist interaction). We will evaluate improvement in nephrologists’ counselling skills by comparing the fidelity between nephrologists counselling LDs in the control versus intervention arms, and by nephrologist sex/gender, using correlations and regressions. Few studies examine adaptations to interventions, which can affect fidelity. We will track types of and reasons for adaptations using Stirman’s FRAME (Framework for Reporting Adaptations and Modifications-Enhanced) via interviews with nephrologists as our team has done previously. Chatbot fidelity metrics will include: number of LDs who launched the chatbot ≥1 time, number of questions asked or information requests submitted and duration (minutes) of chatbot use. We will assess whether the effects of the intervention (ie, LDs’ reduced decisional conflict, increased preparation) vary as a function of fidelity to the intervention (ie, nephrologist and chatbot metrics) using ANCOVA. We will treat EHR integration

### Table 3  Measurement strategy for implementation outcomes

<table>
<thead>
<tr>
<th>Variable/construct</th>
<th>Measure(s)/metrics</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-AIM Implementation Evaluation Framework</td>
<td>Reach</td>
<td>Proportion of LD candidates attending clinic visit who were notified about being potentially eligible for genetic testing/counselling</td>
</tr>
<tr>
<td></td>
<td>Proportion of enrolled LDs (study participants) who were scheduled by the nephrologist for post-test counselling</td>
<td></td>
</tr>
<tr>
<td>Effectiveness (of the APOL1 intervention)</td>
<td>Effect size of the APOL1 testing programme for LDs.</td>
<td>online supplemental file 3</td>
</tr>
<tr>
<td>Adoption</td>
<td>Number and proportion of: 1) ordered APOL1 genetic tests, 2) nephrologists who delivered APOL1 post-test counselling, and 3) nephrologists who engaged in shared decision-making.</td>
<td>EHR Chatbot</td>
</tr>
<tr>
<td>Implementation</td>
<td>Number and proportion of LDs who: 1) used the chatbot, 2) number of questions asked and/or information requests submitted, and 3) duration (minutes) of chatbot use.</td>
<td></td>
</tr>
<tr>
<td>a. Acceptability</td>
<td>Acceptability of Intervention Measure (AIM) 3 items (α=0.85) Survey</td>
<td></td>
</tr>
<tr>
<td>b. Appropriateness</td>
<td>Intervention Appropriateness Measure (IAM) 3 items (α=0.91) Survey</td>
<td></td>
</tr>
<tr>
<td>c. Feasibility</td>
<td>Feasibility of Intervention Measure (FIM) 3 items (α=0.89) Survey</td>
<td></td>
</tr>
<tr>
<td>d. Fidelity</td>
<td>Direct observation (listening) and checklist assessment of counselling sessions Chatbot launch, questions asked/information sought, duration of chatbot use</td>
<td>Observation Chatbot</td>
</tr>
<tr>
<td>Sustainment</td>
<td>Clinical Sustainability Assessment Tool 7 domains (three items each) (Engaged Leadership and Staff; Engaged Stakeholders; Planning and Implementation; Workflow Integration; Monitoring and Evaluation; Organisational Context and Capacity; Outcomes and Effectiveness). It is reliable, usable and valid in a pilot study (n=126) with internal consistencies ranging from (α=0.82–0.89).</td>
<td>Survey</td>
</tr>
</tbody>
</table>

APOL1, Apolipoprotein L1; EHR, electronic health record; LD, living donor.
as an independent variable that may affect the implementation process. Because EHR integration is designed to most proximal support nephrologist behaviours of engaging in post-test counselling and performing SDM, we will examine site-level differences in EHR integration to understand quantitative differences in nephrologist fidelity metrics.

**Sustainability**
At the end of the implementation period, all nephrologists will complete the Clinical Sustainability Assessment Tool to assess preferences and perceptions of factors influencing intervention sustainability.\(^{102}\) The seven domains (three items each) have good internal consistency (\(\alpha\) range=0.84–0.92) and confirmatory factor analysis results demonstrated very good fit of the seven domain structure of the tool.\(^{102}\)

**Increasing nephrologists’ knowledge and skills in APOL1 counselling**
Increasing knowledge and self-efficacy in counselling skills is hypothesised to affect whether they adopt counselling, which will ultimately impact LDs’ outcomes. We will assess practical knowledge and self-efficacy before and after the APOL1 counselling training programme via a 13-item survey, widely used in other provider counselling training programmes\(^{103,104}\); and surveys of beliefs about race (nine items) (\(\alpha=0.61–0.69\)), attributes of race (eight items) (\(\alpha=0.86\)) and genetic variation knowledge (eight items).\(^{106}\) \(H_1\) will be analysed by evaluating increases in practical knowledge and self-efficacy via a Wilcoxon signed-rank test to compare the survey scores on the pretest to the survey scores on the post-test. Due to sample size limitations, we will examine the relationship between changes in knowledge and skill with adoption in a separate analysis, rather than a formal test of mediation, to obtain parameter estimates to power a future study of this mechanistic path.

**Qualitative data analysis**
All audio-recorded focus groups (aim 1) and interviews (aim 2 and aim 3) will be transcribed and analysed for themes emergent from the data\(^{106}\)\(^{107}\) using constant comparison\(^{108}\) and inductive and deductive coding methods.\(^{109}\) Initial codebooks will be developed by establishing deductive codes derived from moderator and interview guide questions. Through an iterative, constant comparative process, research staff will derive inductive codes emergent from the data to stay grounded in the respondent’s point of view by independently reviewing, comparing and openly coding the first set of five transcripts at each site. A series of retreats will be held, whereby staff will compare codes and resolve coding discrepancies in order to refine the codebook until reaching thematic saturation.\(^{110}\)\(^{111}\) All transcripts will be independently coded by at least two research staff and any discrepancies in coding will be resolved through discussion. A summary of each theme will be written by reviewing and comparing all segments of text for a given code across participants/focus groups. Multiple coders and intercoder agreement checks will increase rigour and reliability of the codebook.\(^{112}\) Qualitative data analysis software will aid in coding. We will increase the rigour and reproducibility of qualitative findings via: intermittent member checks with focus group (FG) participants, CAB members and nephrologists to obtain their feedback and verify accuracy of findings, thereby increasing credibility. Using thick description and an audit trail will increase dependability and transferability. Self-reflexivity and triangulation will increase confirmability.\(^{113}\) Results from aim 2 and aim 3 interviews will be used to understand implementation processes and help contextualise aim 3 quantitative results.

**CURRENT STATUS AND PROTOCOL MODIFICATIONS**
To date, we completed adaptation of the Gia chatbot, which involved conducting \(n=10\) focus groups. We also completed adaptation of the APOL1 counselling training programme and obtained approvals to provide Continuing Medical Education and Maintenance of Certification (MOC) credits to nephrologists partaking in the programme, which is anticipated to begin in July 2022. We began recruitment in September 2021 for the LD trial, and as of 13 May, we have obtained informed consent and enrolled \(n=60\) LDs of African ancestry in the control arm. Despite a year of concerted meetings and efforts to identify ways to automate the integration of APOL1 genetic test results directly into Epic, Epic policies pertaining to research and resource limitations at the laboratory prohibited this from occurring, requiring the uploading of faxed results by clinical staff. This change did not impact the research plan as transplant nephrologists still had a mechanism to review results in Epic.

We made several protocol modifications since study inception. With regard to the chatbot, we designed Gia in English but not in Spanish given additional costs involved. Also, per focus group feedback to ensure ample time to complete it prior to the nephrologist visit, Gia would be delivered over 7–12 min rather than 5–7 min, as originally anticipated. We also adapted the educational brochure on APOL1 for nephrologists to hand out to LDs based on updated empirical research and CAB feedback, which is available by request to the corresponding author. The APOL1 counselling training programme did not undergo focus group evaluation because needs assessment interviews and team consultation sufficed to finalise programme content and format, as proposed. However, focus groups were conducted among nephrologists to assess their clinical decision support needs for optimal EHR integration.

Regarding recruitment modifications, recruitment shifted to virtual then hybrid (virtual and in-person) at one site (Georgetown). Additionally, recruitment was slower than anticipated due to COVID-19, hiring delays, adapting the recruitment and implementation strategies for a slower than anticipated due to COVID-19, hiring delays, adapting the recruitment and implementation strategies for a slower than anticipated due to COVID-19, hiring delays, adapting the recruitment and implementation strategies for a slower than anticipated due to COVID-19, hiring delays, adapting the recruitment and implementation strategies for a slower than anticipated due to COVID-19, hiring delays, adapting the recruitment and implementation strategies for a slower than anticipated due to COVID-19, hiring delays, adapting the recruitment and implementation strategies for a slower than anticipated due to COVID-19, hiring delays, adapting the recruitment and implementation strategies for a slower than anticipated due to COVID-19, hiring delays, adapting the recruitment and implementation strategies for a slower than anticipated due to COVID-19, hiring delays, adapting the recruitment and implementation strategies for a slower than anticipated due to COVID-19, hiring delays, adapting the recruitment and implementation strategies for a slower than anticipated due to COVID-19, hiring delays, adapting the recruitment and implementation strategies for a slower than anticipated due to COVID-19, hiring delays, adapting the recruitment and implementation strategies for a slower than anticipated due to COVID-19, hiring delays, adapting the recruitment and implementation strategies for a slower than anticipated due to COVID-19, hiring delays, adapting the recruitment and implementation strategies.
to virtual recruitment, and IRB and contractual delays. Thus, the timeframe for launching the control arm was delayed by 2 months (Northwestern) and 5 months (Georgetown), and the intervention arm was delayed by 2 months (both sites).

Regarding data collection modifications, both nephrologist pretest and post-test counselling discussions with LDs are recorded for LD participants in the control and intervention arms to enable a direct comparison between them due to using an identical assessment strategy. Research staff provided nephrologists a digital recorder to record nephrologist counselling discussions with LDs, rather than observing discussions in person. We adapted the observer checklist to be tailored to the study aims for fidelity monitoring purposes. Additional survey measures are being collected at all time points (e.g., Generalised Anxiety Disorder 7-Item), and current measures are being collected at additional time points for additional situations for both arms. For example, we added Preparedness to Donate to all time points, the Preparation for Decision Making Scale is no longer asked at T1, but asked at T2, T3 and T4, and The Shared Decision-Making Questionnaire is being asked at T2 and T4 in addition to T3.

DISCUSSION

The results of this study will serve as a model for implementing genetic testing and counselling that improves the informed consent of living kidney donor candidates of African ancestry who are at most risk of having two APOL1 risk variants. Because APOL1 risk variants increase LD candidates’ risks of kidney failure post-donation, clinical practice guidelines recommend engaging in counselling, and many ethicists have argued that it is unethical to not inform donor candidates about their risks. Thus, it is essential that LD candidates of African ancestry receive culturally and ethically sound counselling to ensure that they make informed treatment decisions about donating. Ensuring that transplant counselling practices are culturally and ethically sound is especially important because transplant programmes currently vary on their use of counselling and SDM for LD candidates who underwent APOL1 genetic testing.

The model of integration of genetic testing and counselling in this study will be available for dissemination to other transplant programmes in the USA to improve informed decision-making for LD candidates and, thus, foster greater safety in the donation process. Specifically, this will demonstrate an effective strategy for how to scale up genetic counselling services through the use of chatbots to deliver foundational information and training nephrologists to deliver components of genetic counselling and SDM. Furthermore, this model will be important for demonstrating how to integrate genetic test results into the EHR to enhance streamlined clinical decision support for physicians.

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Contributors EJG conceived of the study. EJG, JDS, CW, DD, AS and SD designed the study. EJG, JDS, AA, MC, AG, SD, JS-G, LNM and SD refined the design of intervention implementation. EJG, AA, JS, JF, CW, DD, MC, AG and JS-G contributed to Gia chatbot intervention development. EJG, AA, AS, JF, CY, MC, AG and JS-G contributed to Nephrologist APOL1 Counselling Training Program intervention development. EJG, AA and UR contributed to Epic integration preparation. JDS and EJG collaborated in drafting the manuscript. All authors read, edited, and approved the final version of the manuscript to be published, and agree to be accountable for all aspects of the work.

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