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Practical considerations for *APOL1* genotyping in the living kidney donor evaluation

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Abstract

Background: Association between the apolipoprotein L1 gene (*APOL1*) and nephropathy has altered the epidemiology of chronic kidney disease (CKD). In addition, donor *APOL1* genotypes play important roles in the time to allograft failure in kidneys transplanted from deceased donors and the safety of living kidney donation.

Methods: This manuscript reviews genetic testing for inherited kidney disease in living kidney donors to improve donor safety. *APOL1* genotyping in donors with recent African ancestry is considered.

Results: Based on current data, transplant physicians should discuss *APOL1* genotyping with potential living kidney donors self-reporting recent African ancestry. Until results from *APOL1* Long-term Kidney Transplant Outcomes Network (APOLLO) ancillary studies are available, we present practical approaches from our experience for considering *APOL1* genotyping in the living donor evaluation.

Conclusions: Transplant physicians should inform potential living kidney donors at-risk for *APOL1*-associated nephropathy about the gene and possibility of genetic testing early in the donor evaluation, well before scheduling the donor nephrectomy. Transplant programs must weigh risks of performing a donor nephrectomy in those with two *APOL1* renal-risk variants (high-risk genotypes), particularly younger individuals. Our program counsels kidney donors with *APOL1* high-risk genotypes in the same fashion as with risk genotypes in other nephropathy genes. Because most African American kidney donor candidates lacking hypertension, proteinuria and reduced kidney function after workup will not possess *APOL1* high-risk genotypes, genetic testing is unlikely to markedly increase donor declines and may reassure donors with regard to their long-term kidney outcomes, potentially increasing the number of African American donors.

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Introduction

There is no more powerful gift to a patient with end-stage kidney disease (ESKD) than a kidney transplant. Compared to recipients of a kidney from a deceased donor, those fortunate enough to have a living donor are more likely to remain dialysis-free with functioning allografts for longer durations. Transplant physicians are obligated to provide for the safety and long-term well-being of the living kidney donor. Evaluation of medically complex donors is an inherently challenging process for transplant physicians and can be stressful for donor candidates, recipients and families. The donor nephrectomy is not medically necessary, although it may provide donors with personal and emotional benefits. Donors do not obtain medical benefit and they assume short-term perioperative and long-term medical risk. Although risks are quite low, they are present.[1] Often, there is no perfect donor candidate. Most have minor (or more) considerations. Transplant programs are familiar with the populations they treat, and each program must determine the acceptable level of risk for their living donors.

The current era of genomic medicine has benefitted organ transplantation. It is now relatively simple to screen asymptomatic potential living kidney donors to determine whether they possess risk variants in genes that have known associations with chronic kidney disease (CKD) and consequently avoid donation. This can benefit not only the donor, by preserving their renal mass and hopefully delaying the onset of nephropathy, but also the recipient who might have received a kidney predisposed to more rapid allograft failure. Risks to living kidney donors accrue over many decades. Appreciation of the risk for developing ESKD among former living kidney donors has improved by contrasting their outcomes with those from healthy populations, not the general population where a significant percentage have CKD.[2] Although long-term absolute risk of post donation ESKD are low among donors, relative risk of ESKD is higher in donors and attributable risk is highest in African American donors compared to donors of other ancestries.[3]

The apolipoprotein L1 gene (*APOL1*) association with nondiabetic CKD has transformed nephrology.[4,5] *APOL1* is associated with ESKD in Africans, African Americans, Brazilians and Afro-Caribbeans.[6–8] *APOL1* high-risk genotypes in deceased organ donors (defined as two copies of the G1 and/or G2 renal-risk variants: G1G1, G2G2, or G1G2) also contribute to more rapid failure of kidneys transplanted from African American donors.[9–11] In addition, higher risk for developing post donation CKD in living kidney donors with recent African ancestry, defined as having similar genetic make-up to those currently residing in Africa (*e.g.*, African Americans, Hispanic blacks, Afro-Caribbeans and Africans), has been demonstrated in donors with *APOL1* high-risk genotypes.[12]

There has been increasing awareness among transplant physicians, nephrologists, patients with ESKD and potential living kidney donors about the effects of *APOL1* in kidney transplantation.[13–16] Despite reaching the milestone of equitable proportional rates of deceased donor kidney transplants for African American recipients, significant disparities remain in the incidence of living kidney donor transplants in this population.[17] Rising concerns about higher risks for ESKD in African American donors are likely a major driver of this disparity. The present manuscript reviews the living donor evaluation from the

standpoints of screening for inherited kidney disorders and consideration of *APOL1* genetic testing in individuals with recent African ancestry, including African Americans. Intended for clinicians, it considers associated ethical, social and practical considerations of performing *APOL1* genetic testing.

Screening for inherited kidney diseases in the living donor evaluation

Consideration of genetic counseling and/or testing in living kidney donors is important, underscored by the fact that 40 to 80% of such donors are related to the recipient.[18,19] Genetic susceptibility to kidney disease in potential donors affects their health and well-being and constitutes a risk factor for nephropathy in transplanted kidneys.[20] Cohort studies demonstrate that kidney donation increases the risk for ESKD; however, the absolute risk is low and varies based on ancestry and gender.[1,21,22] Risk for ESKD is generally higher in related, compared to unrelated kidney donors.[2,18]

Transplant teams should inform donor candidates about the potential for genetic predisposition to kidney disease and efforts undertaken to exclude this possibility. This can be challenging because the cause of ESKD in transplant recipients is often unclear; nearly 60% carry a presumptive diagnosis of diabetes or hypertension without histopathological confirmation.[23] Many patients have an alternative (or superimposed) cause of ESKD and lack of an accurate etiology of nephropathy complicates genetic screening of related living donors.[24] A careful family history is critical, but this can also be challenging due to de novo mutations.

Genetic screening techniques often involve sequencing a single suspected gene for pathogenic variants or high throughput methods such as next-generation-sequencing (NGS) to sequence several genes at once. Some laboratories have developed NGS panels to evaluate a given clinical phenotype, such as focal segmental glomerulosclerosis (FSGS).[18,25,26] Genetic testing is simplest in monogenic disorders, but can be challenging for genes with heterogeneous pathology, variable penetrance, or when multiple genes are implicated.[27] Testing for multiple genes can also be a financial burden for transplant programs.

Genetic testing should be considered for kidney donors with a family history of potentially inherited forms of kidney disease in two or more members, whether in the same or different generations. Testing can be considered with one affected first-degree relative, if the extended family history is uncertain. When in doubt, we recommend consultation with a Molecular Genetics Service. Potential donors (and recipients) should be informed that presence of a genetic mutation may not be an absolute contraindication to donation. Factors such as heterozygous versus homozygous gene expression, donor age, absence of signs, symptoms or lack of an abnormal urinalysis could lead to favorable decisions if the estimated risk of kidney disease after donor nephrectomy is deemed acceptable.

Risk of kidney disease in donors whose families have a Mendelian disorder, such as Autosomal Dominant Polycystic Kidney disease (ADPKD) can often be determined based on genetic testing. Mutations in the *PKD1* and *PKD2* genes cause the majority of ADPKD and approximately 50% of affected patients develop ESKD by the age of 60 years.[28–30]

Renal ultrasonography is the most common accepted screening test and can exclude presence of polycystic kidney disease in individuals older than 30 years; however, it has limitations in younger individuals. Magnetic resonance imaging has higher sensitivity and specificity and can be used as a screening test in younger individuals.[31]

Rare forms of Autosomal Dominant Tubulointerstitial Kidney Disease due to uromodulin (*UMOD*), mucin-1 (*MUC1*), renin (*REN*) and hepatocyte nuclear factor-1β (*HNF1B*) gene mutations cause ESKD and can be assessed in potential living-related donors.[32] Podocytopathies such as hereditary FSGS, congenital nephrotic syndrome and steroid resistant nephrotic syndrome are also potential targets for mutation screening in prospective donors whose families have mutations in the nephrin (*NPHS1*), podocin (*NPHS2*), alpha actinin-4 (*ACTN4*), inverted formin-2 (*INF2*) and Wilms tumor-1 (*WT1*) genes, among others.

Genetic screening should be considered in donors whose relatives have atypical hemolytic uremic syndrome associated with mutations in genes that regulate the complement cascade (Table 1).[33,34] Screening can also be performed in donors from families with Alport syndrome (for mutations in the *COL4A3, COL4A4*, and *COL4A5* collagen genes)[35] and Fabry disease (an X-linked lysosomal storage disease that results from deficient α-galactosidase A [α-Gal A] activity due to mutations in the *GLA* gene). Table 1 displays inherited kidney diseases that can be assessed with gene-based techniques in the living donor evaluation.

APOL1 testing in living kidney donor candidates with recent African ancestry

As in native kidney disease, post donation CKD and ESKD are three times higher in African Americans, particularly in younger males, compared to European-derived populations.[19,22,36,37] Living kidney donors often have a family history of ESKD; another established risk factor for future nephropathy.[38] Finally, among donor candidates with risk factors for surgical nephrectomy (*e.g.*, smokers and those with high blood pressure, mildly reduced kidney function or proteinuria), African Americans and Hispanics are less likely to have long-term health insurance necessary to allow for optimal post donation healthcare.[39] *APOL1* plays a key role in the biologic basis for this disparity; however, a minority of individuals with high-risk genotypes will develop CKD. This suggests that a second hit is necessary to develop *APOL1*-associated kidney disease.[40]

Long-term outcomes were assessed in 136 African American living kidney donors from Detroit.[12,41] As in the general population, 14% (19/136) had *APOL1* high-risk genotypes (with 2 renal-risk variants) and 86% low-risk genotypes (0/1 renal-risk variant). Baseline characteristics were similar regardless of *APOL1* genotype. However, mean predonation estimated glomerular filtration rate (eGFR) was significantly lower, albeit not markedly reduced, in those with high-risk genotypes (98±17 ml/min/1.73 m^2 vs. 108±20 in low-risk donors; p=0.03). Of concern, 11% (2/19) of previously healthy kidney donors with *APOL1* high-risk genotypes developed ESKD and 67% developed an eGFR <60 ml/min/1.73 m^2 after 12 year median follow-up. None of the 117 *APOL1* low-risk genotype donors

developed ESKD and only 36% had a follow-up eGFR <60 ml/min/1.73 m^2 (p=0.01). Mean ±SD serum creatinine concentrations at latest follow-up were 1.71±1.2 in *APOL1* high-risk and 1.26+0.3mg/dl in low-risk donors (p=0.003). Other reports reveal *APOL1* high-risk kidney donors can develop post transplant focal segmental glomerulosclerosis progressing to ESKD, along with earlier failure of the transplanted kidney.[8,42,43] These findings raise concern about the safety of live donation from individuals with two *APOL1* renal-risk variants. Based on these case reports, we hypothesize premature transplant failure could also occur in some recipients of *APOL1* high-risk living donor kidneys.

Similar outcomes exist in recipients of deceased donor kidney transplants. Kidneys transplanted from *APOL1* high-risk donors fail more quickly.[11,44] The current Kidney Allocation System downgrades quality in all African American deceased donor kidneys regardless of *APOL1* genotype, although recent data suggest that those with two *APOL1* renal-risk variants (approximately 13%) appear to be at highest risk for early allograft failure.[44] These findings contributed to the need for the prospective National Institutes of Health-supported "*APOL1* Long-term Kidney Transplant Outcomes Network (APOLLO)" and the APOLLO Ancillary Study, "Living Donor Extended Time Outcomes".[45] The American Society of Transplantation and National Kidney Foundation "Kidney Disease Improving Global Outcomes" support additional studies; APOLLO and its ancillary studies will provide these data.[3]

Counseling the living kidney donor candidate about *APOL1*

Until APOLLO results become available, we believe that transplant programs should develop local guidelines to inform potential living kidney donors who self-report recent African ancestry about the role of *APOL1* in kidney disease and outcomes after donation and transplantation (Figure 1). Currently, U.S. transplant programs do not universally test at-risk living donors for *APOL1*, nor do they consider these genotypes in the donor evaluation. For ethical reasons, we feel potential living donors reporting recent African ancestry should be informed that *APOL1* gene testing is commercially available prior to decisions about candidacy.[46,47] Results can be available within 4 hours (in our lab), at low cost and typically paid for by transplant programs. We, and others, consider education about *APOL1* and availability of genetic testing to be the current standard of care.[15,16,36] Kidney donors are not required to undergo genetic testing for *APOL1* (or other genes). Genetic counseling is required when genetic testing is performed; this can provided by the transplant nephrologist or genetic counselor.

Compared to non-African Americans, young African Americans have higher rates of ESKD after donor nephrectomy. We feel it is in the best interest of younger potential donors <50 years of age with *APOL1* high-risk genotypes not to proceed with donation.[12,43] Other programs may choose different age cut-offs. It may prove safer for *APOL1* high-risk individuals to donate a kidney at a later age, when they would more likely have avoided the effects of modifying factors for nephropathy.[40] After age 60, similar long-term renal outcomes exist in European American and African American living kidney donors.[37] This supports that 60 years of age may be a reasonable cut-off for use of *APOL1* risk stratification in medically eligible donors (education about *APOL1* and testing should still

be provided). It remains uncertain how to counsel potential donors 50 to 60 years of age. We suggest donor candidates and their physician have a frank discussion carefully weighing all elements of donor risk and benefit. Some programs may be comfortable accepting donors in their 50's if they are otherwise medically acceptable, but data are lacking. Extrapolating retrospective results from Doshi et al.,[12] a 51-year old African American donor with two *APOL1* renal-risk variants might face up to an 11% risk for ESKD and 67% chance of eGFR <60 ml/min/1.73 m^2 by 63 years of age. Based on this, we do not currently advocate that these individuals donate a kidney.

Medically acceptable donors who refuse to undergo *APOL1* testing but wish to donate regardless of their own inherent risk for developing ESKD could proceed to nephrectomy, as long as their transplant program provided clear information about *APOL1*, kidney disease and transplant outcomes. We suggest documenting these discussions in the medical record.

APOL1 and sickle cell testing is performed at our program and others, to assist with risk-stratification of potential living kidney donors who self-report recent African ancestry.[48] We recognize that a small percentage of donors who report as non-African could still possess *APOL1* renal-risk variants due to African ancestry they were unaware of or did not report. However, we do not feel it is cost-effective to screen them. In chromosomes from healthy European Americans, 0.3% possessed a single *APOL1* renal-risk variant; two renal-risk variants were extremely rare.[49] The *APOL1* association with nephropathy has much in common with the hemoglobin S gene variant (*HbS*) association with sickle cell disease. A single risk *HbS* or *APOL1* variant (autosomal dominant) protects from malarial and trypanosomal infection, respectively. Risk variants are common and more often present in certain ancestral groups. Inheriting two copies of a risk variant (autosomal recessive inheritance) is required to develop sickle cell disease or CKD. In contrast to *HbS*, where individuals with risk genotypes will develop sickle cell disease, approximately 20% with *APOL1* high-risk genotypes develop nephropathy (personal communication, Dr. Martin Pollak). Prior to the donor evaluation, most individuals with sickle cell trait presenting to our center are aware of their status because testing is performed at birth in North Carolina.

To date, our experience with *APOL1* testing in living kidney donors has been positive. Potential donors first submit screening packets highlighting their medical history and listing medications. Prior to the in-person medical evaluation, our program records height, weight and blood pressure and performs a urinalysis and urine protein testing. Donors from distant locations have laboratory studies and a 24-hour urine prior to medical evaluations. We typically do not proceed with the evaluation of African American living donors who have hypertension (systolic blood pressures above 140 mmHg or diastolic pressures above 90 mmHg), an eGFR that is abnormal for their age, proteinuria (spot urine protein:creatinine ratio >200 mg/g) or other concerning features during work-up. In this fashion, exclusions for kidney disease typically occur prior to discussions about *APOL1* testing as many individuals with *APOL1* high-risk genotypes screen out due to low eGFR or proteinuria.

Performing the donor workup in this sequence excludes many individuals with recent African ancestry likely to have *APOL1* high-risk genotypes without formal genetic testing. In turn, individuals who proceed to the full clinical evaluation with discussion of genetic

testing are at lower risk for *APOL1*-nephropathy compared to the general population. The percentage of donor candidates screened at our program and found to have two *APOL1* renal-risk variants is very low. Although we cannot fully mitigate the long-term risks from hypertension and diabetes in African American donors, they are counseled about long-term medical risks, 24-hour ambulatory blood pressure monitoring is performed when indicated, and glucose tolerance testing is currently performed on all potential donors.

Ethical considerations

Ethical concerns involving genetic testing for *APOL1* have been reported.[50–52] Candidates who present for living donor evaluations do not all face the same long-term risk for CKD and it is the transplant program's responsibility to evaluate each donor to the best of their ability. It is evident that *APOL1* renal-risk variants are virtually limited to individuals with recent African ancestry. We contend that offering *APOL1* testing to these individuals and considering results in donor selection should not differ from other genetic tests employed in the evaluation of living donors. In our opinion, claims of discrimination do a disservice to the African American community. Individuals who request information about *APOL1* and elect to have testing performed should have been aware (prior to ordering the test) that those with high-risk genotypes are at increased risk for CKD. In our practice, they are informed that factors beyond genetic make-up contribute to risk for kidney disease, including dietary factors, smoking, lack of exercise and failure to maintain ideal body weight. Prior to the test being ordered they should be aware that no specific therapies for *APOL1*-kidney disease currently exist.

APOL1 testing is a scientific breakthrough; this gene displays the most powerful genetic association in common complex disease. In our view, transplant programs should provide information on *APOL1* and offer testing to those with self-reported recent African ancestry. Advisory councils comprised of African Americans with kidney disease, former kidney donors, relatives of patients with ESKD and general populations espouse similar views about genetic testing and return of results, even when treatments are not available.[16,53] The number of African American living kidney donors has been declining in recent years.[54] Although future rates of living kidney donation are unknown, informing potential kidney donors that they lack *APOL1* high-risk genotypes might provide them reassurance. We believe this information could increase the numbers of African American living kidney donors in the future. In addition, it has the potential to reduce the excess risk for post donation ESKD in African American living kidney donors, relative to European American. As new treatments for native *APOL1*-nephropathy are developed, they may prove useful in the transplant setting.[55]

Conclusions

Kidney transplant programs evaluating African American living donor candidates should become familiar with the effects of *APOL1* and consider offering *APOL1* and non-*APOL1* genetic testing. If programs lack individuals comfortable with these processes, other transplant programs and/or Clinical Laboratory Improvement Amendments-certified *APOL1* labs could assist. Prospective results from the APOLLO Study will ideally clarify best

practices. Until then, we recommend education about *APOL1* in kidney disease and the offer of genetic testing in kidney donor candidates who self-report recent African ancestry. Our program does not typically proceed with living kidney donation from individuals with two *APOL1* renal-risk variants under the age of 60 years. In addition, we treat *APOL1* genetic data in a similar fashion as genotypes for other inherited kidney diseases. We provide education, offer genetic testing and counseling. In our opinion, these practices provide potential kidney donors with the ability to make the most informed and safest decision.

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References

1. Muzaale AD, Massie AB, Wang MC, et al. Risk of end-stage renal disease following live kidney donation. JAMA. 2014;311(6):579–586. [PubMed: 24519297]
2. Lentine KL, Lam NN, Segev DL. Risks of Living Kidney Donation: Current State of Knowledge on Outcomes Important to Donors. Clin J Am Soc Nephrol. 2019;14(4):597–608. [PubMed: 30858158]
3. Lentine KL, Kasiske BL, Levey AS, et al. Summary of Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors. Transplantation. 2017;101(8):1783–1792. [PubMed: 28737659]
4. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science. 2010;329(5993):841–845. [PubMed: 20647424]
5. Tzur S, Rosset S, Shemer R, et al. Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. Hum Genet. 2010;128(3): 345–350. [PubMed: 20635188]
6. Riella C, Siemens TA, Wang M, et al. APOL1-Associated Kidney Disease in Brazil. Kidney Int Rep. 2019;4(7):923–929. [PubMed: 31317114]
7. Kasembeli AN, Duarte R, Ramsay M, et al. APOL1 Risk Variants Are Strongly Associated with HIV-Associated Nephropathy in Black South Africans. J Am Soc Nephrol. 2015;26(11):2882–2890. [PubMed: 25788523]
8. Kofman T, Audard V, Narjoz C, et al. APOL1 polymorphisms and development of CKD in an identical twin donor and recipient pair. Am J Kidney Dis. 2014;63(5):816–819. [PubMed: 24518129]
9. Reeves-Daniel AM, Depalma JA, Bleyer AJ, et al. The APOL1 Gene and Allograft Survival after Kidney Transplantation. Am J Transplant. 2011;11(5):1025–1030. [PubMed: 21486385]
10. Freedman BI, Julian BA, Pastan SO, et al. Apolipoprotein L1 gene variants in deceased organ donors are associated with renal allograft failure. Am J Transplant. 2015;15(6):1615–1622. [PubMed: 25809272]
11. Freedman BI, Pastan SO, Israni AK, et al. APOL1 Genotype and Kidney Transplantation Outcomes From Deceased African American Donors. Transplantation. 2016;100(1):194–202. [PubMed: 26566060]
12. Doshi MD, Ortigosa-Goggins M, Garg AX, et al. APOL1 Genotype and Renal Function of Black Living Donors. J Am Soc Nephrol. 2018;29(4):1309–1316. [PubMed: 29339549]
13. Cohen DM, Mittalhenkle A, Scott DL, et al. African American living-kidney donors should be screened for APOL1 risk alleles. Transplantation. 2011;92(7):722–725. [PubMed: 21878839]

14. Newell KA, Formica RN, Gill JS, et al. Integrating APOL1 Gene Variants Into Renal Transplantation: Considerations Arising From the American Society of Transplantation Expert Conference. Am J Transplant. 2017;17(4):901–911. [PubMed: 27997071]
15. Riella LV, Sheridan AM. Testing for High-Risk APOL1 Alleles in Potential Living Kidney Donors. Am J Kidney Dis. 2015;66(3):396–401. [PubMed: 26049628]
16. Umeukeje EM, Young BA, Fullerton SM, et al. You Are Just Now Telling Us About This? African American Perspectives of Testing for Genetic Susceptibility to Kidney Disease. J Am Soc Nephrol. 2019;30(4):526–530. [PubMed: 30858224]
17. Jay CL, Cigarroa FG. Disparities in Live Donor Kidney Transplantation: Related to Poverty, Race, or Ethnicity? JAMA. 2018;319(1):24–26. [PubMed: 29297060]
18. Thomas CP, Mansilla MA, Sompallae R, et al. Screening of Living Kidney Donors for Genetic Diseases Using a Comprehensive Genetic Testing Strategy. Am J Transplant. 2017;17(2):401–410. [PubMed: 27434427]
19. Lentine KL, Schnitzler MA, Garg AX, et al. Race, Relationship and Renal Diagnoses After Living Kidney Donation. Transplantation. 2015;99(8):1723–1729. [PubMed: 25905980]
20. Allen PJ, Chadban SJ, Craig JC, et al. Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes. Kidney Int. 2017;92(2):461–469. [PubMed: 28601198]
21. Grams ME, Sang Y, Levey AS, et al. Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate. N Engl J Med. 2016;374(5):411–421. [PubMed: 26544982]
22. Lentine KL, Schnitzler MA, Xiao H, et al. Racial variation in medical outcomes among living kidney donors. N Engl J Med. 2010;363(8):724–732. [PubMed: 20818874]
23. Sharma SG, Bomback AS, Radhakrishnan J, et al. The modern spectrum of renal biopsy findings in patients with diabetes. Clin J Am Soc Nephrol. 2013;8(10):1718–1724. [PubMed: 23886566]
24. Tucker BM, Freedman BI. Need to Reclassify Etiologies of ESRD on the CMS 2728 Medical Evidence Report. Clin J Am Soc Nephrol. 2018;13(3):477–479. [PubMed: 29042463]
25. Biesecker LG, Green RC. Diagnostic clinical genome and exome sequencing. N Engl J Med. 2014;371(12):1170.
26. Brown EJ, Pollak MR, Barua M. Genetic testing for nephrotic syndrome and FSGS in the era of next-generation sequencing. Kidney Int. 2014;85(5):1030–1038. [PubMed: 24599252]
27. McCarthy HJ, Bierzynska A, Wherlock M, et al. Simultaneous sequencing of 24 genes associated with steroid-resistant nephrotic syndrome. Clin J Am Soc Nephrol. 2013;8(4):637–648. [PubMed: 23349334]
28. Rossetti S, Hopp K, Sikkink RA, et al. Identification of gene mutations in autosomal dominant polycystic kidney disease through targeted resequencing. J Am Soc Nephrol. 2012;23(5):915–933. [PubMed: 22383692]
29. Simms RJ, Travis DL, Durkie M, et al. Genetic testing in the assessment of living related kidney donors at risk of autosomal dominant polycystic kidney disease. Transplantation. 2015;99(5): 1023–1029. [PubMed: 25340609]
30. Huang E, Samaniego-Picota M, McCune T, et al. DNA testing for live kidney donors at risk for autosomal dominant polycystic kidney disease. Transplantation. 2009;87(1):133–137. [PubMed: 19136903]
31. Pei Y, Hwang YH, Conklin J, et al. Imaging-based diagnosis of autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 2015;26(3):746–753. [PubMed: 25074509]
32. Eckardt KU, Alper SL, Antignac C, et al. Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management-A KDIGO consensus report. Kidney Int. 2015;88(4): 676–683. [PubMed: 25738250]
33. George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Engl J Med. 2014;371(7): 654–666. [PubMed: 25119611]
34. Bu F, Maga T, Meyer NC, et al. Comprehensive genetic analysis of complement and coagulation genes in atypical hemolytic uremic syndrome. J Am Soc Nephrol. 2014;25(1):55–64. [PubMed: 24029428]
35. Kashtan CE, Ding J, Garosi G, et al. Alport syndrome: a unified classification of genetic disorders of collagen IV alpha345: a position paper of the Alport Syndrome Classification Working Group. Kidney Int. 2018;93(5):1045–1051. [PubMed: 29551517]

36. Cherikh WS, Young CJ, Kramer BF, et al. Ethnic and gender related differences in the risk of end-stage renal disease after living kidney donation. Am J Transplant. 2011;11(8):1650–1655. [PubMed: 21672160]
37. Wainright JL, Robinson AM, Wilk AR, et al. Risk of ESRD in prior living kidney donors. Am J Transplant. 2018;18(5):1129–1139. [PubMed: 29392849]
38. Freedman BI, Spray BJ, Tuttle AB, et al. The familial risk of end-stage renal disease in African Americans. Am J Kidney Dis. 1993;21(4):387–393. [PubMed: 8465818]
39. Rodrigue JR, Fleishman A. Health Insurance Trends in United States Living Kidney Donors (2004 to 2015). Am J Transplant. 2016;16(12):3504–3511. [PubMed: 27088263]
40. Freedman BI, Skorecki K. Gene-gene and gene-environment interactions in apolipoprotein L1 gene-associated nephropathy. Clin J Am Soc Nephrol. 2014;9(11):2006–2013. [PubMed: 24903390]
41. Freedman BI, Julian BA. Evaluation of Potential Living Kidney Donors in the APOL1 Era. J Am Soc Nephrol. 2018;29(4):1079–1081. [PubMed: 29523593]
42. Servais A, Gribouval O, Gaillard F, et al. APOL1 risk genotype in Europe: Data in patients with focal segmental glomerulosclerosis and after renal transplantation. Nephrol Ther. 2019;15 Suppl 1:S85–s89. [PubMed: 30981401]
43. Zwang NA, Shetty A, Sustento-Reodica N, et al. APOL1-Associated End-Stage Renal Disease in a Living Kidney Transplant Donor. Am J Transplant. 2016;16(12):3568–3572. [PubMed: 27588375]
44. Julian BA, Gaston RS, Brown WM, et al. Effect of Replacing Race With Apolipoprotein L1 Genotype in Calculation of Kidney Donor Risk Index. Am J Transplant. 2017;17(6):1540–1548. [PubMed: 27862962]
45. Freedman BI, Moxey-Mims M. The APOL1 Long-Term Kidney Transplantation Outcomes Network-APOLLO. Clin J Am Soc Nephrol. 2018;13(6):940–942. [PubMed: 29703792]
46. Young BA, Fullerton SM, Wilson JG, et al. Clinical Genetic Testing for APOL1: Are We There Yet? Semin Nephrol. 2017;37(6):552–557. [PubMed: 29110763]
47. Ross LF, Thistlethwaite JR Jr. Introducing Genetic Tests With Uncertain Implications in Living Donor Kidney Transplantation: ApoL1 as a Case Study. Prog Transplant. 2016;26(3):203–206. [PubMed: 27302054]
48. Naik RP, Irvin MR, Judd S, et al. Sickle Cell Trait and the Risk of ESRD in Blacks. J Am Soc Nephrol. 2017;28(7):2180–2187. [PubMed: 28280138]
49. Cooke JN, Bostrom MA, Hicks PJ, et al. Polymorphisms in MYH9 are associated with diabetic nephropathy in European Americans. Nephrol Dial Transplant. 2012;27(4):1505–1511. [PubMed: 21968013]
50. Mohan S, Iltis AS, Sawinski D, et al. APOL1 Genetic Testing in Living Kidney Transplant Donors. Am J Kidney Dis. 2019.
51. Gordon EJ, Wicklund C, Lee J, et al. A National Survey of Transplant Surgeons and Nephrologists on Implementing Apolipoprotein L1 (APOL1) Genetic Testing Into Clinical Practice. Prog Transplant. 2018:1526924818817048.
52. Gordon EJ, Amórtegui D, Blancas I, et al. African American Living Donors' Attitudes About APOL1 Genetic Testing: A Mixed Methods Study. Am J Kidney Dis. 2018;72(6):819–833. [PubMed: 30360961]
53. Freedman BI, Fletcher AJ, Sanghani VR, et al. Perceptions regarding genetic testing in populations at risk for nephropathy. Am J Nephrol. 2013;38(6):453–457. [PubMed: 24280773]
54. Al Ammary F, Bowring MG, Massie AB, et al. The changing landscape of live kidney donation in the United States from 2005 to 2017. Am J Transplant. 2019.
55. Aghajan M, Booten SL, Althage M, et al. Antisense oligonucleotide treatment ameliorates IFN-gamma-induced proteinuria in APOL1-transgenic mice. JCI Insight. 2019;4(12).

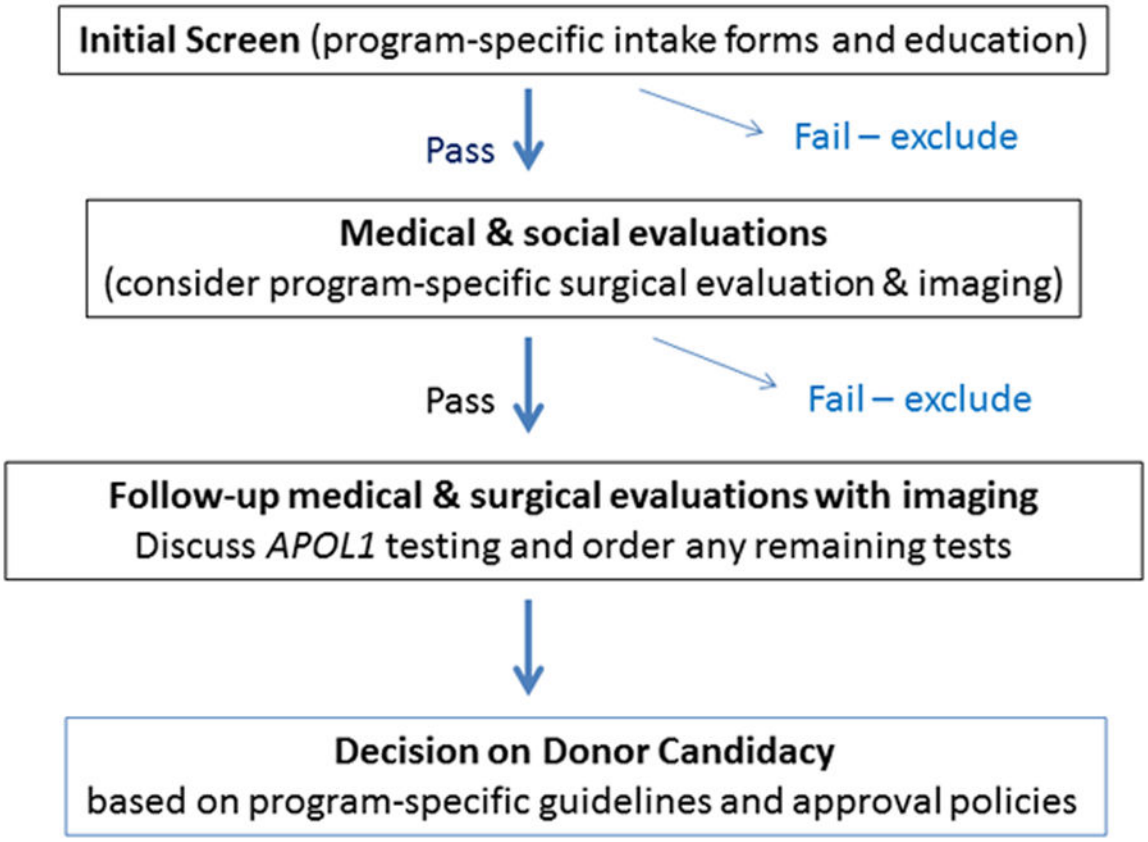

Figure 1.
Sample flow chart for evaluation of African American living kidney-donor candidates.

Table 1.

Inherited kidney disorders suitable for genetic screening

Disorder	Mode of inheritance	Implicated genes
Polycystic Kidney Disease	Autosomal dominant	*PKD1, PKD2*
Atypical Hemolytic Uremic Syndrome	Autosomal dominant *	*CFB, CFH, MCP, CFI, C3*
Alport syndrome	Autosomal recessive X-linked for *COLA5*	*COL4A3, COL4A4, COL4A5*
Fabry disease	X-linked	*GLA*
Tubulointerstitial kidney disease	Autosomal dominant	*UMOD, MUC1, REN, HNF1B*
Focal segmental glomerulosclerosis (FSGS)/steroid resistant nephrotic syndrome	Autosomal dominant	*ACTN4, INF2, TRPC6, NPHS1, NPHS2***
Solidified glomerulosclerosis/FSGS (if recent African ancestry present)	Autosomal recessive	*APOL1*

* Autosomal recessive transmission with specific mutations have been identified.

** Additional genes implicated