Kidney360

Clinical Applications of Genetic Discoveries in Kidney Transplantation: a Review

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Abstract
Growth in knowledge of the genetics of kidney disease has revealed that significant percentages of patients with diverse types of nephropathy have causative mutations. Genetic testing is poised to play an increasing role in the care of patients with kidney disease. The role of genetic testing in kidney transplantation is not well established. This review will explore the ways in which genetic testing may be applied to improve the care of kidney transplant recipients and donors.

Introduction
The genetics of kidney disease has undergone explosive growth in recent years due to significant advances in sequencing technology and genetics methodology (1,2). Recent data suggest that significant percentages of patients with nephropathy have causative monogenic variants underlying their disease (3,4). The role of genetic testing in the clinical practice of kidney transplantation is relatively undefined. However, given the growth of the field, genetic testing is poised to play a larger role in the evaluation and management of both transplant recipients and donors. This review will explore the ways in which genetic testing may improve care in kidney transplantation.

Genetics of Kidney Disease
Knowledge of the genetic basis of kidney disease has expanded dramatically in recent years, driven by rapid advances in genetic technologies. The cost of sequencing the entire human genome has dropped dramatically from an estimated $100 million in 2001 to approximately $1000 in 2017 (5) due to the development of next-generation sequencing, a collection of techniques that involve the rapid, parallel sequencing of DNA fragments followed by computational analysis to assemble the source sequence. Whole-exome sequencing (WES) is a comprehensive mode of testing by next-generation sequencing that involves sequencing only the exome, the approximately 2% of the genome which encompasses most mutations known to cause human disease. WES now costs as little as approximately $1000 or less in clinical settings, which compares favorably with many other tests and procedures used routinely in transplantation. WES offers the advantage of allowing for the analysis of an unlimited number of genes at the time of testing, or in the future when subsequent genes of interest may be discovered (6).

To date, mutations in >500 genes have been implicated in causing various forms of kidney disease (3,7). These mutations, although individually rare, are in aggregate relatively common among patients with kidney disease. Several recent papers have demonstrated that a significant proportion of both pediatric and adult patients with nephropathy have causative genetic variants. Mallet et al. (8) used a series of targeted gene panels to evaluate 135 families with familial renal disease; genetic diagnoses were made in 58 families (43%) across a range of diagnoses. Lata et al. (9) selected 92 patients out of 344 referred to Columbia University for evaluation of noncystic kidney disease. The authors identified diagnostic mutations in 24% of the patients using WES and evaluation of 287 genes associated with nephropathy. A follow-up study examined a larger cohort of >3000 mostly adult patients with a diverse array of kidney diseases, who were not necessarily selected for characteristics likely to suggest genetic disease. Nonetheless, diagnostic mutations were identified in 9% of the patients overall, including 24% of those with congenital or cystic diseases and 17% of those with unknown cause. Similarly, Mann et al. (10) examined a cohort of 102 pediatric transplant recipients. Using WES, a genetic cause for nephropathy was identified in >30% of the patients. Connaughton et al. performed WES on 138 adults from 114 families in a multicenter study in Ireland. Overall, a genetic diagnosis was made in 37% of patients (4). The rate of diagnosis was 15% even in patients who had neither extrarenal manifestations nor family history of nephropathy. Among patients with unknown etiology of kidney disease, the diagnostic rate was 47%. Collectively these recent data show that monogenic causes of kidney disease are relatively common. The data also identify subsets of patients enriched for causative genetic mutations, such as those with unknown cause of kidney disease and those with family history.

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Role of Genetic Testing in Kidney Transplantation

Genetic testing has three main applications in clinical kidney transplantation: the risk assessment of donors, disease characterization of recipients, and improving drug selection and dosing for recipients using pharmacogenomic data.

Living Donors

A central challenge of living donor kidney transplantation involves estimating the postnephrectomy risk of the donor with regard to subsequently developing kidney disease, hypertension, or other diseases (11). Recent large-scale studies have shown that although donors have generally excellent outcomes, nephrectomy may confer a several-fold increase in risk of ESKD (11–13). Those studies suggest that risks may be higher for donors who are related to their recipients (14,15), which implies that genetic factors are relevant. The use of genetic data is likely to improve estimates of risk to donors who are related to recipients or who otherwise have family history of nephropathy.

The Organ Procurement and Transplantation Network (OPTN) policy for the medical evaluation of living kidney donors states that "hospitals must develop and comply with a written protocol for polycystic kidney disease or other inherited renal disease as indicated by family history" (16). Similarly, the Kidney Disease Improving Global Outcomes guidelines (17) state that "transplant programs should have a strategy for evaluating for inherited kidney disease in donor candidates when there is a family history of kidney failure and the recipient's cause of kidney failure is uncertain." Further, when the donor is related to the recipient, the cause of recipient ESKD should be determined whenever possible. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines enumerate several specific diseases which, when present in the family history, should trigger consideration of genetic testing of donors due to high rates of causative mutations, including FSGS, atypical hemolytic uremic syndrome, Alport disease, sickle cell trait, and autosomal dominant tubulointerstitial kidney disease. Because patients with nephropathy of a variety of etiologies are increasingly recognized to have high rates of causative genetic mutations (see above), compliance with the OPTN and KDIGO policies imply that genetic testing should be commonplace. The University of Iowa recently published a description of their experience with a program of genetic testing in donors with family history of kidney disease using a targeted panel of nephropathy genes (18). Several cases were described in which genetic testing allowed for selection of donors confirmed to lack disease-causing alleles present in affected family members. In addition, two recent papers have urged consideration of genetic testing in prospective donors with family history of potentially monogenic forms of ESKD as described in the KDIGO guidelines (19,20).

Two situations in which genetics affect donor suitability and which are commonly encountered merit additional discussion: donors with family history of cystic kidney disease, and donors of African ancestry who may have high-risk *APOL1* alleles.

Cystic Kidney Disease Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic form of kidney disease, affecting an estimated 1:500 to 1:1000 individuals. Patients with cystic kidney disease represent approximately 12% of recipients in the United States, and 18% of living donor recipients (21). Thus, prospective donors with family members with cystic disease are frequently encountered. Most ADPKD is caused by a mutation in either the *polycystic kidney disease 1* (*PKD1*) or *PKD2* gene. The genotype is predictive of the clinical course and can be used to exclude disease presence on clinical grounds. For example, in families with a *PKD1* mutation, the absence of any renal cyst by the age of 30 provides almost complete certainty of disease exclusion (22,23). However, in families with a *PKD2* mutation or an unknown genotype, ADPKD cannot be excluded by imaging until the age of 40. Because most patients with ADPKD still do not have genetic testing at the time of ESKD, our institution's clinical practice is thus to screen all prospective familial donors with negative imaging under the age of 40 with genetic testing. Genetic testing (generally done by WES or Sanger sequencing) requires identification of the PKD mutation in the recipient, followed by testing for the familial mutation in the donor.

Multiple genes besides *PKD1* and *PKD2* can cause a cystic phenotype mimicking ADPKD (24); thus ADPKD may be misdiagnosed and imaging criteria for excluding the presence of disease in prospective donors may be unreliable. Therefore, it is important to have a relatively low threshold to order genetic testing when the affected patient does not conform to the classic ADPKD presentation of bilaterally uniformly enlarged, massively cystic kidneys (23,25).

APOL1 Nephropathy *APOL1* is the gene encoding apo L-1 (ApoL1). Recently, two risk alleles for nephropathy, termed G1 and G2, were identified in populations of African ancestry (26). Patients who are homozygous for the risk alleles have substantially increased risk of developing ESKD (27) from a variety of different causes including HIV-associated nephropathy and hypertension. The risk seems to be associated with ApoL1 expression in the kidney itself rather than in other tissues. For example, several papers have reported that homozygous *APOL1* risk alleles in donors are associated with worse allograft survival (28–30), whereas the *APOL1* genotype of the recipient does not seem to affect allograft outcomes (31). APOL1 risk alleles likely explain at least in part why African American donors exhibit higher rates of subsequent development of ESKD (14,15). The mechanism by which *APOL1* risk alleles increase the incidence of ESKD is not known, and most patients with two risk alleles never develop ESKD. However, a recent study (32) of 136 African American donors revealed that donors with a high-risk genotype (two risk alleles) had lower eGFR both pre- and postdonation, and demonstrated a faster rate of eGFR decline postdonation compared with donors with zero or one risk allele. A larger study (called APOL1 Long-term Kidney Transplantation Outcomes Network; APOLLO) of the effects of *APOL1* genetics on kidney donors (and recipients) has started enrolling patients and should yield more precise data on the issue (33). At present, due to the lack of precise data on the implications of ApoL1 genotypes, there is debate as to whether donors of recent African ancestry should undergo *APOL1* genotyping. Several expert groups have recommended educating prospective donors about *APOL1* alleles and offering testing to those who choose to pursue it (19,20,34,35). A recent survey

of transplant centers in the United States revealed that about half of centers offer *APOL1* testing to black donors (36). Further, Julian *et al.* (37) have proposed that, with regard to deceased donors, ApoL1 genotype should replace race in the calculation of Kidney Donor Risk Index, which predicts longevity of the allograft and is used in organ allocation decisions. This interesting suggestion seeks a more granular assessment of organ quality from African American donors, but it would require rapid genotyping of deceased donors and will require further research before widespread implementation.

Of note, evidence exists for the presence of other susceptibility alleles for kidney disease in addition to *ApoL1*, particularly for diabetic nephropathy (38) and for IgA nephropathy (39). Before consideration of incorporation of these susceptibility alleles into clinical practice, additional research to define the magnitude (and hopefully mechanisms) of the risks will be required, as is ongoing for *ApoL1* alleles.

Recipients

The genetic testing of prospective kidney transplant recipients is useful in many cases. As discussed above, in patients with a living related donor, identification of causative mutations in the recipient is used to guide subsequent testing and interpretation of donor genotypes. This approach aligns with the KDIGO recommendation to determine the cause of ESKD in recipients with living related donors whenever possible.

Genetic diagnoses may be psychologically beneficial to patients seeking transplant, many of whom have no clear explanation for ESKD. Genetic diagnoses are useful to family members of the patient and help facilitate their early evaluation and treatment. Unlike renal biopsies, genetic data can be informative even after ESKD has developed. Indeed, in their program Schrezenmeier *et al.* (40) have reported genetic testing on patients who are waitlisted for a transplant under the age of 40 with unknown cause of nephropathy. Using targeted gene panel testing, they identified pathogenic mutations in 15 of 81 patients (19%).

Genetic testing in transplant synergizes with overall trends in health care toward the provision of more individualized care (41). Recipients are expected to experience more tailored post-transplant care due to genetic testing. For example, the finding of a mutation in a type IV collagen gene in a patient with FSGS would reduce concerns about recurrent disease after transplantation and may result in reduced follow-up testing. Genetic diagnoses often point to the likelihood of disease in other organ systems and prompt referral and evaluation, for example to an audiologist in a patient with collagen mutations.

Some medical centers are beginning large-scale WES of patients across their health care system (42), motivated in part by the expectation that ≥3% may be found to have one of approximately 60 actionable mutations identified by the American College of Medical Genetics and Genomics (43). This collection of highly penetrant alleles confers significant risk for a variety of cardiac, metabolic, and oncologic diseases which may benefit from early discovery and management. Knowledge of the presence of these alleles is relevant to post-transplant care of affected recipients.

Another benefit of increased genetic testing on transplant recipients is that it will yield rich sources of data for future research. When coupled with detailed phenotypic and clinical data available for patients receiving a transplant, investigation into the genetic basis of both kidney disease and transplant outcomes is possible. iGeneTRAiN is a consortium encompassing genetic data on patients who have received a transplant from >45 genetic studies (44,45). Studies from this data set promises to advance the understanding of not only genetic causes of kidney disease, but also genetic determinants of rejection and allograft survival. For example, a growing body of research from the iGeneTRAiN and others suggest that allelic mismatches outside of HLA genes between kidney donors and recipients can have important implications for allograft outcomes (46–48). The larger availability of WES data on donor and recipient pairs will advance these studies.

Pharmacogenomics

Another growing area for the use of genetics in recipients of a kidney transplant is pharmacogenomics, the study of how genes affect how a patient responds to medications. The two transplant medications for which there is clear pharmacogenomics data are tacrolimus and azathioprine. The Clinical Pharmacogenetics Implementation Consortium has guideline recommendations for both drugs and is an excellent reference for practitioners (49,50).

Tacrolimus is the most commonly prescribed immunosuppressant medication postkidney transplant (51) and variations in the gene *CYP3A5* are well known to affect tacrolimus levels in patients after receiving a transplant. *CYP3A5*1* is the functional allele, with loss-of-function variants including *3, *6, and *7. Based on the alleles a patient carries, the patient can be classified into three phenotypes: extensive metabolizer, intermediate metabolizer, and poor metabolizer (49). A meta-analysis found an association between *CYP3A5*1* expressors and acute rejection but did not find an association with acute or chronic nephrotoxicity (52). Strategies that incorporate pharmacogenetic data into tacrolimus dose selection have been developed and shown to shorten the time to target tacrolimus levels in new transplant patients (53).

Azathioprine was approved by the Food and Drug Administration in 1968 and has a range of uses including kidney transplantation and autoimmune diseases. The gene product of *TMPT*, thiopurine s-methyltransferase (TPMT), allows azathioprine to be degraded from a toxic to a nontoxic metabolite. Similar to *CYP3A5*, patients can carry a functional *TPMT* allele (*1) or loss-of-function alleles (*2, *3A, *3B, *3C, *4), leading to normal or high TPMT activity, intermediate activity, or deficient activity (50). Knowledge of *TMPT* alleles (and thus TPMT activity) can be used to tailor azathioprine dose to avoid toxicity. Studies have demonstrated the cost benefit of *TPMT* testing in patients with irritable bowel disease and rheumatologic disorders (54,55).

Several additional genes with variant alleles are relevant to the metabolism of medications commonly taken by patients who have received a transplant including *NUDT15* (azathioprine), *CYP2C19* (clopidogrel and voriconazole), *CYP2D6* (codeine, oxycodone, tramadol, tricyclic

antidepressants), *CYP2C19* (trycyclic antidepressants), and *HLA-B* (allopurinol). Multigene tests are available to simultaneously type multiple pharmacogenetic loci for similar cost to traditional typing of the *TMPT* gene alone (56). Unfortunately, insurance coverage may not yet be available for multigene tests in many instances.

Implementation of Genetic Testing in a Clinical Kidney Transplantation Program and Future Research

Genetic testing in the evaluation of kidney disease is a rapidly developing field. As discussed above, available guidelines from the OPTN and KDIGO imply that genetic testing in renal transplant should become more widespread, particularly in the evaluation of living donors with family history of nephropathy. There is so far only scant literature on how renal transplant centers are incorporating genetic testing into clinical practice (18,40).

The implementation of genetic testing in transplant centers requires attention to several evolving issues including reimbursements for genetic testing and privacy concerns (*e.g.*, sharing genetic results from a recipient with a prospective related donor). Informed consent for genetic testing ideally allows for future use of the data in research. Further, the interpretation of genetic data requires significant expertise from both geneticists and nephrologists. The list of nephropathy genes is evolving, as is the list of causative mutations. Complicating matters further, some mutations previously identified as causative may be reconsidered in light of subsequent reports (57). The clinical significance of identified mutations is not always unambiguous. For example, in autosomal recessive Alport syndrome, the significance of heterozygous mutations in family members of the affected individual requires integration of clinical, familial, and genetic factors (58,59).

Despite these difficulties, given the high rates of genetic causes of nephropathy (3,4,10), genetic testing of patients receiving transplants is expected to offer clinical benefit. The clearest clinical benefit is to donors related to recipients, where genetic testing may be able to rule out presence of a causative allele in the donor (18). Thus, at our center, we are beginning to apply WES to all approved recipients who do not have an obvious secondary cause of ESKD (*e.g.*, diabetic nephropathy or drug toxicity) and who have prospective living related donors. For recipients found to have causative mutations in a set of evaluated nephropathy genes, prospective related donors are screened for the identified mutation. Our goal is to identify donors who may harbor alleles that put them at unacceptable risk for developing nephropathy. Costs for genetic testing are generally a small fraction of the total cost of recipient and donor evaluations and are commonly covered by insurance. Genetic counseling is provided by members of the clinical genetics team and/or the transplant nephrologist. In addition, recipients are characterized by a pharmacogenomics gene chip, which identifies alleles relevant to the metabolism of several drugs used in patients who have received a transplant, including tacrolimus and azathioprine. Pharmacogenetic data are incorporated into the electronic health record and are automatically recalled when relevant medications are prescribed in the system.

Research is needed to quantify the positive and negative effects of genetic testing on donors and recipients. Important research questions include determining the fraction of donors and recipients whose clinical care was meaningfully affected by genetic data, characterizing the cost of genetic testing in monetary terms as well as in disruptions to the pretransplant evaluation, and delineating of the appropriate criteria to identify patients likely to benefit from testing. The benefits of pharmacogenetics have not been well established regarding clinical kidney transplant outcomes such as rejection, graft survival, episodes of drug toxicity, and hospitalization rates. However, as pharmacogenetic testing becomes cheaper and more accessible, it will facilitate the performance of the necessary studies.

The genetics of kidney disease will continue to evolve as knowledge grows and genotyping technology becomes more powerful. The kidney transplant community will need to determine the best ways to incorporate these advances into improving the care of transplant donors and recipients.

References

1. Devuyst O, Knoers NV, Remuzzi G, Schaefer F; Board of the Working Group for Inherited Kidney Diseases of the European Renal Association and European Dialysis and Transplant Association: Rare inherited kidney diseases: Challenges, opportunities, and perspectives. *Lancet* 383: 1844–1859, 2014
2. Hildebrandt F: Decade in review--genetics of kidney diseases: Genetic dissection of kidney disorders. *Nat Rev Nephrol* 11: 635–636, 2015
3. Groopman EE, Marasa M, Cameron-Christie S, Petrovski S, Aggarwal VS, Milo-Rasouly H, Li Y, Zhang J, Nestor J, Krithivasan P, Lam WY, Mitrotti A, Piva S, Kil BH, Chatterjee D, Reingold R, Bradbury D, DiVecchia M, Snyder H, Mu X, Mehl K, Balderes O, Fasel DA, Weng C, Radhakrishnan J, Canetta P, Appel GB, Bomback AS, Ahn W, Uy NS, Alam S, Cohen DJ, Crew RJ, Dube GK, Rao MK, Kamalakaran S, Copeland B, Ren Z, Bridgers J, Malone CD, Mebane CM, Dagaonkar N, Fellström BC, Haefliger C, Mohan S, Sanna-Cherchi S, Kiryluk K, Fleckner J, March R, Platt A, Goldstein DB, Gharavi AG: Diagnostic utility of exome sequencing for kidney disease. *N Engl J Med* 380: 142–151, 2019
4. Connaughton DM, Kennedy C, Shril S, Mann N, Murray SL, Williams PA, Conlon E, Nakayama M, van der Ven AT, Ityel H, Kause F, Kolvenbach CM, Dai R, Vivante A, Braun DA, Schneider R, Kitzler TM, Moloney B, Moran CP, Smyth JS, Kennedy A, Benson K, Stapleton C, Denton M, Magee C, O'Seaghdha CM, Plant WD, Griffin MD, Awan A, Sweeney C, Mane SM, Lifton RP, Griffin B, Leavey S, Casserly L, de Freitas DG, Holian J, Dorman A, Doyle B, Lavin PJ, Little MA, Conlon PJ, Hildebrandt F: Monogenic causes of chronic kidney disease in adults. *Kidney Int* 95: 914–928, 2019
5. Wetterstrand KA: The cost of sequencing a human genome. Bethesda, MD, National Human Genome Research Institute, 2019. Available at: https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost. Accessed March 18, 2020
6. Yang Y, Muzny DM, Reid JG, Bainbridge MN, Willis A, Ward PA, Braxton A, Beuten J, Xia F, Niu Z, Hardison M, Person R,

Bekheirnia MR, Leduc MS, Kirby A, Pham P, Scull J, Wang M, Ding Y, Plon SE, Lupski JR, Beaudet AL, Gibbs RA, Eng CM: Clinical whole-exome sequencing for the diagnosis of mendelian disorders. *N Engl J Med* 369: 1502–1511, 2013

7. Groopman EE, Rasouly HM, Gharavi AG: Genomic medicine for kidney disease. *Nat Rev Nephrol* 14: 83–104, 2018

8. Mallett AJ, McCarthy HJ, Ho G, Holman K, Farnsworth E, Patel C, Fletcher JT, Mallawaarachchi A, Quinlan C, Bennetts B, Alexander SI: Massively parallel sequencing and targeted exomes in familial kidney disease can diagnose underlying genetic disorders. *Kidney Int* 92: 1493–1506, 2017

9. Lata S, Marasa M, Li Y, Fasel DA, Groopman E, Jobanputra V, Rasouly H, Mitrotti A, Westland R, Verbitsky M, Nestor J, Slater LM, D'Agati V, Zaniew M, Materna-Kiryluk A, Lugani F, Caridi G, Rampoldi L, Mattoo A, Newton CA, Rao MK, Radhakrishnan J, Ahn W, Canetta PA, Bomback AS, Appel GB, Antignac C, Markowitz GS, Garcia CK, Kiryluk K, Sanna-Cherchi S, Gharavi AG: Whole-exome sequencing in adults with chronic kidney disease: a pilot study [published correction appears in Ann Intern Med 168: 308, 2018]. *Ann Intern Med* 168: 100–109, 2018

10. Mann N, Braun DA, Amann K, Tan W, Shril S, Connaughton DM, Nakayama M, Schneider R, Kitzler TM, van der Ven AT, Chen J, Ityel H, Vivante A, Majmundar AJ, Daga A, Warejko JK, Lovric S, Ashraf S, Jobst-Schwan T, Widmeier E, Hugo H, Mane SM, Spaneas L, Somers MJG, Ferguson MA, Traum AZ, Stein DR, Baum MA, Daouk GH, Lifton RP, Manzi S, Vakili K, Kim HB, Rodig NM, Hildebrandt F: Whole-exome sequencing enables a precision medicine approach for kidney transplant recipients. *J Am Soc Nephrol* 30: 201–215, 2019

11. 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* 14: 597–608, 2019

12. Muzaale AD, Massie AB, Wang MC, Montgomery RA, McBride MA, Wainright JL, Segev DL: Risk of end-stage renal disease following live kidney donation. *JAMA* 311: 579–586, 2014

13. Mjøen G, Hallan S, Hartmann A, Foss A, Midtvedt K, Øyen O, Reisæter A, Pfeffer P, Jenssen T, Leivestad T, Line PD, Øvrehus M, Dale DO, Pihlstrøm H, Holme I, Dekker FW, Holdaas H: Long-term risks for kidney donors. *Kidney Int* 86: 162–167, 2014

14. Massie AB, Muzaale AD, Luo X, Chow EKH, Locke JE, Nguyen AQ, Henderson ML, Snyder JJ, Segev DL: Quantifying post-donation risk of ESRD in living kidney donors. *J Am Soc Nephrol* 28: 2749–2755, 2017

15. Wainright JL, Robinson AM, Wilk AR, Klassen DK, Cherikh WS, Stewart DE: Risk of ESRD in prior living kidney donors. *Am J Transplant* 18: 1129–1139, 2018

16. Organ Procurements and Transplantation Network: Organ procurement and transplantation network policies. 2019. Available at: https://optn.transplant.hrsa.gov/governance/policies. Accessed October 16, 2019

17. Lentine KL, Kasiske BL, Levey AS, Adams PL, Alberú J, Bakr MA, Gallon L, Garvey CA, Guleria S, Li PK, Segev DL, Taler SJ, Tanabe K, Wright L, Zeier MG, Cheung M, Garg AX: KDIGO clinical practice guideline on the evaluation and care of living kidney donors. *Transplantation* 101[8S Suppl 1]: S1–S109, 2017

18. Thomas CP, Mansilla MA, Sompallae R, Mason SO, Nishimura CJ, Kimble MJ, Campbell CA, Kwitek AE, Darbro BW, Stewart ZA, Smith RJ: Screening of living kidney donors for genetic diseases using a comprehensive genetic testing strategy. *Am J Transplant* 17: 401–410, 2017

19. Neugut YD, Mohan S, Gharavi AG, Kiryluk K: Cases in precision medicine: APOL1 and genetic testing in the evaluation of chronic kidney disease and potential transplant [published online ahead of print Oct 8, 2019]. *Ann Intern Med*

20. Mena-Gutierrez AM, Reeves-Daniel AM, Jay CL, Freedman BI: Practical considerations for APOL1 genotyping in the living kidney donor evaluation. *Transplantation* 104: 27–32, 2020

21. Hart A, Smith JM, Skeans MA, Gustafson SK, Wilk AR, Castro S, Robinson A, Wainright JL, Snyder JJ, Kasiske BL, Israni AK: OPTN/SRTR 2017 annual data report: Kidney. *Am J Transplant* 19[Suppl 2]: 19–123, 2019

22. Pei Y, Watnick T: Diagnosis and screening of autosomal dominant polycystic kidney disease. *Adv Chronic Kidney Dis* 17: 140–152, 2010

23. Cornec-Le Gall E, Alam A, Perrone RD: Autosomal dominant polycystic kidney disease. *Lancet* 393: 919–935, 2019

24. Cornec-Le Gall E, Torres VE, Harris PC: Genetic Complexity of autosomal dominant polycystic kidney and liver diseases. *J Am Soc Nephrol* 29: 13–23, 2018

25. Cornec-Le Gall E, Chebib FT, Madsen CD, Senum SR, Heyer CM, Lanpher BC, Patterson MC, Albright RC, Yu AS, Torres VE, Harris PC; HALT Progression of Polycystic Kidney Disease Group Investigators: The value of genetic testing in polycystic kidney diseases illustrated by a family with PKD2 and COL4A1 mutations. *Am J Kidney Dis* 72: 302–308, 2018

26. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, Bowden DW, Langefeld CD, Oleksyk TK, Uscinski Knob AL, Bernhardy AJ, Hicks PJ, Nelson GW, Vanhollebeke B, Winkler CA, Kopp JB, Pays E, Pollak MR: Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 329: 841–845, 2010

27. Parsa A, Kao WH, Xie D, Astor BC, Li M, Hsu CY, Feldman HI, Parekh RS, Kusek JW, Greene TH, Fink JC, Anderson AH, Choi MJ, Wright JT Jr, Lash JP, Freedman BI, Ojo A, Winkler CA, Raj DS, Kopp JB, He J, Jensvold NG, Tao K, Lipkowitz MS, Appel LJ; AASK Study Investigators; CRIC Study Investigators: APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med* 369: 2183–2196, 2013

28. Freedman BI, Pastan SO, Israni AK, Schladt D, Julian BA, Gautreaux MD, Hauptfeld V, Bray RA, Gebel HM, Kirk AD, Gaston RS, Rogers J, Farney AC, Orlando G, Stratta RJ, Mohan S, Ma L, Langefeld CD, Bowden DW, Hicks PJ, Palmer ND, Palanisamy A, Reeves-Daniel AM, Brown WM, Divers J: APOL1 genotype and kidney transplantation outcomes from deceased African American donors. *Transplantation* 100: 194–202, 2016

29. Freedman BI, Julian BA, Pastan SO, Israni AK, Schladt D, Gautreaux MD, Hauptfeld V, Bray RA, Gebel HM, Kirk AD, Gaston RS, Rogers J, Farney AC, Orlando G, Stratta RJ, Mohan S, Ma L, Langefeld CD, Hicks PJ, Palmer ND, Adams PL, Palanisamy A, Reeves-Daniel AM, Divers J: Apolipoprotein L1 gene variants in deceased organ donors are associated with renal allograft failure. *Am J Transplant* 15: 1615–1622, 2015

30. Reeves-Daniel AM, DePalma JA, Bleyer AJ, Rocco MV, Murea M, Adams PL, Langefeld CD, Bowden DW, Hicks PJ, Stratta RJ, Lin JJ, Kiger DF, Gautreaux MD, Divers J, Freedman BI: The APOL1 gene and allograft survival after kidney transplantation. *Am J Transplant* 11: 1025–1030, 2011

31. Lee BT, Kumar V, Williams TA, Abdi R, Bernhardy A, Dyer C, Conte S, Genovese G, Ross MD, Friedman DJ, Gaston R, Milford E, Pollak MR, Chandraker A: The APOL1 genotype of African American kidney transplant recipients does not impact 5-year allograft survival. *Am J Transplant* 12: 1924–1928, 2012

32. Doshi MD, Ortigosa-Goggins M, Garg AX, Li L, Poggio ED, Winkler CA, Kopp JB: APOL1 genotype and renal function of black living donors. *J Am Soc Nephrol* 29: 1309–1316, 2018

33. Freedman BI, Moxey-Mims M: The APOL1 long-term kidney transplantation outcomes network-APOLLO. *Clin J Am Soc Nephrol* 13: 940–942, 2018

34. Newell KA, Formica RN, Gill JS, Schold JD, Allan JS, Covington SH, Wiseman AC, Chandraker A: Integrating APOL1 gene variants into renal transplantation: Considerations arising from the American society of transplantation expert conference. *Am J Transplant* 17: 901–911, 2017

35. Ross LF, Thistlethwaite JR Jr: Introducing genetic tests with uncertain implications in living donor kidney transplantation: ApoL1 as a case study. *Prog Transplant* 26: 203–206, 2016

36. McIntosh T, Mohan S, Sawinski D, Iltis A, DuBois JM: Variation of ApoL1 testing practices for living kidney donors. *Prog Transplant* 30: 22–28, 2020

37. Julian BA, Gaston RS, Brown WM, Reeves-Daniel AM, Israni AK, Schladt DP, Pastan SO, Mohan S, Freedman BI, Divers J: Effect of replacing race with apolipoprotein L1 genotype in calculation of kidney donor risk Index. *Am J Transplant* 17: 1540–1548, 2017

38. Guo J, Rackham OJL, Sandholm N, He B, Österholm AM, Valo E, Harjutsalo V, Forsblom C, Toppila I, Parkkonen M, Li Q, Zhu W, Harmston N, Chothani S, Öhman MK, Eng E, Sun Y, Petretto E, Groop PH, Tryggvason K: Whole-genome sequencing of finnish type 1 diabetic siblings discordant for kidney disease reveals DNA variants associated with diabetic nephropathy. *J Am Soc Nephrol* 31: 309–323, 2020

39. Neugut YD, Kiryluk K: Genetic determinants of IgA nephropathy: Western perspective. *Semin Nephrol* 38: 443–454, 2018

40. Schrezenmeier E, Budde K, Bergmann C: Diagnostic utility of exome sequencing for kidney disease. *N Engl J Med* 380: 2078, 2019

41. Murray MF: The path to routine genomic screening in health care. *Ann Intern Med* 169: 407–408, 2018

42. Trivedi BP: Medicine's future? *Science* 358: 436–440, 2017

43. Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, Herman GE, Hufnagel SB, Klein TE, Korf BR, McKelvey KD, Ormond KE, Richards CS, Vlangos CN, Watson M, Martin CL, Miller DT: Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): A policy statement of the American College of Medical Genetics and Genomics [published correction appears in Genet Med 19: 484, 2017]. *Genet Med* 19: 249–255, 2017

44. International Genetics & Translational Research in Transplantation Network (iGeneTRAiN): Design and implementation of the international genetics and translational research in transplantation Network. *Transplantation* 99: 2401–2412, 2015

45. Fishman CE, Mohebnasab M, van Setten J, Zanoni F, Wang C, Deaglio S, Amoroso A, Callans L, van Gelder T, Lee S, Kiryluk K, Lanktree MB, Keating BJ: Genome-wide study updates in the international genetics and translational research in transplantation Network (iGeneTRAiN). *Front Genet* 10: 1084, 2019

46. Yang JY, Sarwal MM: Transplant genetics and genomics. *Nat Rev Genet* 18: 309–326, 2017

47. Reindl-Schwaighofer R, Heinzel A, Kainz A, van Setten J, Jelencsics K, Hu K, Loza BL, Kammer M, Heinze G, Hruba P, Koňaříková A, Viklicky O, Boehmig GA, Eskandary F, Fischer G, Claas F, Tan JC, Albert TJ, Patel J, Keating B, Oberbauer R; iGeneTRAiN consortium: Contribution of non-HLA incompatibility between donor and recipient to kidney allograft survival: Genome-wide analysis in a prospective cohort. *Lancet* 393: 910–917, 2019

48. Mesnard L, Muthukumar T, Burbach M, Li C, Shang H, Dadhania D, Lee JR, Sharma VK, Xiang J, Suberbielle C, Carmagnat M, Ouali N, Rondeau E, Friedewald JJ, Abecassis MM, Suthanthiran M, Campagne F: Exome sequencing and prediction of long-term kidney allograft function. *PLOS Comput Biol* 12: e1005088, 2016

49. Birdwell KA, Decker B, Barbarino JM, Peterson JF, Stein CM, Sadee W, Wang D, Vinks AA, He Y, Swen JJ, Leeder JS, van Schaik R, Thummel KE, Klein TE, Caudle KE, MacPhee IA: Clinical pharmacogenetics implementation consortium (CPIC) guidelines for CYP3A5 genotype and tacrolimus dosing. *Clin Pharmacol Ther* 98: 19–24, 2015

50. Relling MV, Schwab M, Whirl-Carrillo M, Suarez-Kurtz G, Pui CH, Stein CM, Moyer AM, Evans WE, Klein TE, Antillon-Klussmann FG, Caudle KE, Kato M, Yeoh AEJ, Schmiegelow K, Yang JJ: Clinical pharmacogenetics implementation consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. *Clin Pharmacol Ther* 105: 1095–1105, 2019

51. Hart A, Smith JM, Skeans MA, Gustafson SK, Wilk AR, Robinson A, Wainright JL, Haynes CR, Snyder JJ, Kasiske BL, Israni AK: OPTN/SRTR 2016 annual data report: Kidney. *Am J Transplant* 18 [Suppl 1]: 18–113, 2018

52. Rojas L, Neumann I, Herrero MJ, Bosó V, Reig J, Poveda JL, Megías J, Bea S, Aliño SF: Effect of CYP3A5*3 on kidney transplant recipients treated with tacrolimus: A systematic review and meta-analysis of observational studies. *Pharmacogenomics J* 15: 38–48, 2015

53. Thervet E, Loriot MA, Barbier S, Buchler M, Ficheux M, Choukroun G, Toupance O, Touchard G, Alberti C, Le Pogamp P, Moulin B, Le Meur Y, Heng AE, Subra JF, Beaune P, Legendre C: Optimization of initial tacrolimus dose using pharmacogenetic testing. *Clin Pharmacol Ther* 87: 721–726, 2010

54. Winter J, Walker A, Shapiro D, Gaffney D, Spooner RJ, Mills PR: Cost-effectiveness of thiopurine methyltransferase genotype screening in patients about to commence azathioprine therapy for treatment of inflammatory bowel disease. *Aliment Pharmacol Ther* 20: 593–599, 2004

55. Marra CA, Esdaile JM, Anis AH: Practical pharmacogenetics: The cost effectiveness of screening for thiopurine s-methyltransferase polymorphisms in patients with rheumatological conditions treated with azathioprine. *J Rheumatol* 29: 2507–2512, 2002

56. Chua EW, Cree SL, Ton KN, Lehnert K, Shepherd P, Helsby N, Kennedy MA: Cross-comparison of exome analysis, next-generation sequencing of amplicons, and the iPLEX(®) ADME PGx panel for pharmacogenomic profiling. *Front Pharmacol* 7: 1, 2016

57. Wang M, Chun J, Genovese G, Knob AU, Benjamin A, Wilkins MS, Friedman DJ, Appel GB, Lifton RP, Mane S, Pollak MR: Contributions of rare gene variants to familial and sporadic FSGS. *J Am Soc Nephrol* 30: 1625–1640, 2019

58. Petzold F, Bachmann A, Bergmann C, Helmchen U, Halbritter J: Retrospective genetic analysis illustrates the spectrum of autosomal Alport syndrome in a case of living-related donor kidney transplantation. *BMC Nephrol* 20: 340, 2019

59. Girimaji N, Murugan Sm S, Nada R, Sharma A, Rathi M, Kohli HS, Gupta KL, Ramachandran R: Successful renal transplantation in a family with a novel mutation in COL4A3 gene and autosomal recessive Alport syndrome [published online ahead of print Jan 10, 2020]. *Nephrology (Carlton)* doi:10.1111/nep.13693