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Pretransplant Genetic Testing of Live Kidney Donors at Risk for Autosomal Dominant Polycystic Kidney Disease

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Autosomal dominant polycystic kidney disease (ADPKD) affects approximately 12 million individuals worldwide and is the fourth most common cause of end-stage renal disease (ESRD) in the US. Compared with a non-diabetic ESRD cohort, ADPKD patients are more likely to receive a renal transplant and have a significant survival advantage detectable four years after transplantation (1, 2). Factors responsible for these benefits are not established, but may include better general health and high levels of motivation and familial support. Nevertheless, 5000 patients with polycystic kidney disease remain on the renal transplant waiting list because of an insufficient number of donors (3). Some potential living related donors are ineligible because the ADPKD diagnosis cannot be definitively excluded. Limitations in our understanding of the PKD phenotype and genotype contribute to this uncertainty and are barriers to successful renal transplantation. What are some of these limitations and how can they be overcome?

ADPKD is causedin ~85% of patients by a mutation of the PKD1 gene; the remainder are caused by a PKD2 mutation (4, 5). The pathogenesis of ADPKD has been attributed to a “two-hit” phenomenon, with somatic and germline mutations combining to inactivate the PKD gene (6). These loss of function mutations promote excessive proliferation of renal tubular epithelia, manifested as cyst formation and chronic kidney disease (7). Despite its monogenic inheritance, the ADPKD phenotype is characterized by intrafamilial and interfamilial variability that is attributed to allelic and locus heterogeneity, respectively (8). Compared with PKD2 patients, those with PKD1 mutations progress to ESRD 20 years earlier and die at a younger age (8). Moreover, patients with mutations in the 5’ region of PKD1 develop ESRD earlier and are more prone to intracranial aneurysms than those with 3’ mutations(9, 10). Modifying loci contribute to the variable clinical expression of ADPKD (11).

The diagnosis of ADPKD requires an age-specific cystic renal phenotype and a 50% risk of inheritance, determined by a positive family history. These criteria were defined 15 years ago using ultrasonography to detect renal cysts in patients with PKD1 mutations (12). The diagnostic sensitivity is ~90% between ages 15–30 years and 100% for older patients. By contrast, in PKD2 patients younger than 30 years, renal ultrasonographic criteria have a sensitivity of only 67% (13). Diagnostic criteria have not been established for other imaging modalities with higher resolution for kidney cysts (i.e., magnetic resonance imaging [MRI],

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computerized tomography [CT]). However, the diagnostic and prognostic information that could be provided by MRI is apparent from the analysis of a prospective cohort (14). In that study, renal cysts developed earlier in PKD1 than PKD2 patients and this evidently represents agene-specific characteristic, whereas the cyst growth rate was similar in PKD1 and PKD2 patients. Mean total kidney volume, which partly reflects cyst volume, was greater in PKD1 and was associated with the rate of progression of kidney failure.

Genetic testing, either by linkage analysis or by direct sequencing, can establish the ADPKD diagnosis, but each technique has impediments to its use. Linkage analysis requires multiple affected and unaffected family members. Although a family history of ADPKD was elicited from 90% of affected patients in a university-based prospective cohort, one would anticipate a lower rate in clinical practice (15). In that case, direct PKD gene sequencing would be required, with its higher cost and longer turnaround time for reporting results. Moreover, the high prevalence of polymorphisms and private mutations, particularly in PKD1, obscures the identification of pathogenic genetic changes (16, 17). Consequently, the diagnosis is established unequivocally by gene sequencing in only about one-half of all cases. Computational methods can increase the detection rate for pathogenic PKD gene sequence variants, but these are not well established and, thus, are not used routinely for clinical decision-making in ADPKD (16, 17).

The failure to confirm or exclude the diagnosis of ADPKD has broad implications for both the donor and recipient, especially when the prospective donor is a young family member, in whom ultrasonography is less likely to be definitive. In the current issue of *Transplantation*, Huang et al. attempt to provide a diagnostic strategy that is based upon genetic testing of live kidney donors at 50% risk for ADPKD in whom renal imaging studies are inconclusive (18). First, the prospective recipient undergoes PKD gene testing. If a PKD gene mutation is identified, then directed genetic testing of the donor follows. A donor is ineligible if the genetic test is positive. If the mutation is not found in the donor, then the diagnosis of ADPKD is excluded and transplantation can proceed. If the recipient's genetic test is indeterminate, then genotyping of the donor is not performed and donation is deferred.

Several benefits may result from this strategy. It is likely to increase the number of renal transplants from a living related donor because genotyping should confirm eligibility of donors without ADPKD who would otherwise be excluded by their equivocal renal imaging results. In others, it will uncover previously undiagnosed ADPKD, highlighting their need for surveillance by a nephrologist. Moreover, as genetic testing is applied to a broader population, additional mutations will be identified, thereby improving the diagnostic sensitivity of genetic testing methods.

Although genetic testing will surely become the standard for ADPKD diagnosis, the proposal by Huang et al. raises several issues that warrant consideration before it can be applied to the pretransplant evaluation. The diagnostic sensitivity of direct sequencing is relatively low, especially for the PKD1 gene, because it is highly polymorphic and genetic variants of unknown pathogenic potential are commonly reported for each patient. Thus, genetic counseling would become a critical component of the pretransplant evaluation to

confirm that test results are correctly reported and interpreted, and to ensure that appropriate treatment decisions ensue (19). The details of this process are not defined by the authors.

Genetic testing in this algorithm would become one of the most expensive components of the pretransplant evaluation, as the cost of PKD gene sequencing currently exceeds $5,000 (including the recipient and one donor). A relatively high prevalence of non-diagnostic test results is anticipated because of its limited sensitivity. The authors justify this expense by asserting that the annual cost of care after transplantation is about 25% that of dialysis; the net savings should far exceed the cost of genotyping. Nevertheless, they acknowledge that the cost of this strategy could not be defined because no data exist regarding the number of potential donors who were excluded by an uncertain ADPKD diagnosis. By their estimate, the number of additional transplants would not be very high. A complete cost-benefit analysis could not be provided; it is reasonable to expect this information before establishing a new health care policy.

Renal imaging is a key element of this algorithm. Although the same cyst number criteria were used by the authors for each modality (i.e., ultrasonography, MRI, CT), these criteria have only been validated for ultrasonography (12)and cannot be assumed to apply uniformly to other imaging methods. If CT or MRI provides more definitive diagnostic information than ultrasonography, then fewer donors would need genetic testing. Given the current limitations of genetic testing methods, a more rigorous analysis of the diagnostic criteria for MRI and CT is required to reduce the ambiguity of this algorithm. The necessary data are likely to be found in existing patient data repositories.

Renal transplantation is currently the best available treatment for ESRD in ADPKD, but it remains out of reach for many. The proposal by Huang et al. to integrate genetic testing with the pretransplant evaluation is important because it attempts to enhance our understanding of the ADPKD phenotype and genotype. Advancements in genetic testing and renal imaging methods will improve diagnostic strategies and, ultimately, increase access to kidney transplantation.

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