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See related article, "A Randomized Study Comparing Parathyroidectomy with Cinacalcet for Treating Hypercalcemia in Kidney Allograft Recipients with Hyperparathyroidism," on pages 2487–2494.

The End of Racial Disparities in Kidney Transplantation? Not So Fast!

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There is a long-standing perception among the transplant community that blacks and generally other ethnic minorities are disadvantaged with respect to the opportunity for and outcomes after kidney transplantation. The evidence in support of this supposition is well documented, but the discussion of solutions to racial disparities in kidney transplantation is a complicated one because of the complexity of the issues. Basically, they can be parsed into three categories:

(*1*) The issue of access to care, delay in referral for transplant evaluation, and subsequent delay in access to the national waiting list in the United States for kidney transplantation.
(*2*) Issues related to the distribution of a scarce resource—kidney organ allocation.
(*3*) Issues related to the outcomes after kidney transplantation.

Disparities between racial groups have been documented in all of these categories. For example, in one of the first large studies to examine racial variation in the stepwise process to achieve a kidney transplant (KT), multiple sequential barriers to blacks were identified.[1] These included the initial referral for transplant evaluation, next being approved and then finally being placed on the national kidney waitlist. The comparative rates of those receiving their first kidney transplant in this study revealed 35% less transplants for eligible blacks when compared to white recipients.

It is important to note that the issues listed in all three categories above often overlap. For example, KT outcomes can strongly be influenced by the length of time that a patient spends on dialysis and the waiting list: increasing duration of dialysis time has been shown to have a negative effect on transplant allograft survival.[2] Therefore, getting on the waitlist (an access issue) and the time that transpires before receiving a kidney offer (waiting time; an allocation issue) can conspire to affect KT outcome.

In over two decades of reporting on health disparities across many fields of medicine, often, the major emphasis has been on the social determinants of health—access to care, between-group socioeconomic status, types and quality of insurance coverage, educational level of attainment, and so forth; all strong correlates of health outcomes, which usually flagged the disadvantage of poverty and the attendant paucity of resources as strong predictors of poor outcomes. Recently, however, genetic contribution to ESRD risk and its potential bearing on racial differences in native kidney disease expression and KT outcomes have come into greater focus—more on this later.

The study by Purnell *et al.*[3] in this issue of the *Journal of the American Society of Nephrology* suggests that the gap between blacks and whites in kidney allograft survival—an outcome measure—is narrowing significantly. This, arguably, is one of the most important measures of health disparity in ESRD management and runs counter to one of the longest standing observations differentiating black versus white transplant recipients. Using a large United States national data registry—the Scientific Registry of Transplant Recipients—Purnell *et al.*[3] examined KT outcomes over the past two decades. The analysis was stratified by race and broken down into an early cohort—follow-up from 1990 to 1992—and three contemporary time periods as comparisons beginning in 2007. The findings are encouraging: there was substantial improvement in kidney graft survival for both black deceased donor (DD) and live donor (LD) KT recipients. In what can be termed the early cohort period, black DD kidney recipients experienced an approximate 40% higher rate of 5-year kidney graft loss compared with white DD KT recipients. By contrast, the late cohorts showed a marked decline in the rate of graft loss for blacks. DD KT graft loss in these groups fell from 40% to 10% higher rate of graft loss compared with white DD recipients: not a complete elimination of the risk of graft loss for black recipients but a dramatic 75% reduction. Notably, in the late cohorts, there were no significant differences in outcomes for LD KT recipients between groups.

Therefore, can we now declare victory and hail the extinction of racial disparities in kidney transplantation? Not so fast! The outcomes of kidney allograft survival represent only one category by which disparities between racial groups in transplantation should be measured. We need to make a comprehensive assessment of all of the areas in which disparities in kidney transplantation can be addressed.

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One might argue, therefore, that we are making the mistake of looking for answers in all of the usual places but missing new important information. Where else should we look?

The question of biology—is this the basis for an irreducible disparities gap or new untapped opportunities?

GENES MAY HAVE A POWERFUL INFLUENCE ON KT SURVIVAL (OUTCOMES)

Emerging data from the human genome beg the hypothetical question of whether we may be close to an irreducible gap in KT outcomes between blacks and other racial groups as a function of important and heretofore, unexplored biologic differences.[4] It is now well known that two genetic variants at the *APOL1* locus rose to high frequency in sub-Saharan Africa because of their conferring protection against the epidemic Trypanosomiasis (African Sleeping Sickness). By mechanisms still not well understood, they also predispose black individuals with that genomic signature to increased risk for nondiabetic CKD.[5,6] The independent sequence variants, G1 and G2 in the *APOL1* gene, account for most of the excess risk of ESRD among blacks, whose risk of ESRD is 3.3 times that of whites.[7] It is also noteworthy that black KT recipients who are homozygous for the G1 and G2 *APOL1* gene variants also have earlier allograft failure than individuals who are wild type or heterozygous at these loci.[8] The question is whether these genetic determinants, segregating in the black population, have an outsized influence on long-term KT longevity, despite innovations in immunosuppression and surgical technique, improved post-transplant medication adherence (the issue of compliance), and general post-transplant care.

BIOLOGY MAY ALSO HAVE A LARGE INFLUENCE ON ORGAN DISTRIBUTION (ALLOCATION)

The second example of a biologic barrier originates in the population biology of blood group differences between racial groups. Blood type B is a relatively rare blood type, and therefore, patients with blood type B tend to wait longer for kidneys and have been transplanted at a lower rate than candidates of any other blood group.[9] Because blood type B candidates are most commonly ethnic minorities (approximately 70%), the disparity in transplant rates for recipients with this blood group contributes to the overall lower transplant rates for minority patients. Type A is a common blood group in the donor population. Previous research has shown that type A donors with two specific subtypes (A_2 and A_2B) are compatible with blood type B candidates with low levels ($<$1:8 titer) of natural anti-A antibodies, thus providing these candidates with additional transplant opportunities.[10]

Recently, the findings were highlighted of the first United Network for Organ Sharing/Organ Procurement and Transplantation Network (OPTN/UNOS) Minority Affairs Committee–sponsored variance of practice study, an investigation that was designed to conduct a geographically diverse and larger-scale study of the efficacy of transplanting blood groups A_2 and A_2B DD kidneys into blood group B recipients. The results show equal graft survival between the test groups and their B-to-B control counterparts. Furthermore, there was an estimated 10% overall increase in the rate of minority transplantation if this system were to be fully adopted.[11] As noted in the report, by April of 2015, only 3.6% of active B candidates in the United States had been registered to accept potential A_2/A_2B offers. Clearly, many more B candidates could be listed for the A_2/A_2B option than currently are taking advantage of it, potentially resulting in a substantial increase in minority transplant opportunities.[11]

The issue of biologic differences between populations affecting disparities in KT is not new. As noted by Purnell *et al.*,[3] the OPTN/UNOS policy decision to eliminate priority allocation points by HLA-B antigen status (2003) has led to a roughly 20% reduction in disparity in the rates of DD KT between minority and white recipients and reduction in waiting time for minorities as well as improved KT outcomes for these patients.[12] Clearly, biologic factors can have a potent effect on both allocation and KT outcomes after transplantation; the two examples above overlap in this regard.

CLOSING THE DISPARITIES GAP

For Access

Closing the disparities gap in transplantation depends heavily on complementary health policy initiatives–multipronged strategies moving in parallel. A good example here is the recent adoption of the provision of waitlisting at the time of GFR decline $\leq$20 ml/min. This rule triggers the automatic accrual of waiting time on listing even before but including the time of dialysis initiation and helps circumvent the barrier of first being referred. However, patients and their health care providers need to be educated about such options to take full advantage of them. Such policies increase equity and uphold the ethical Principle of Justice in organ allocation.[13] Through a variety of public health initiatives, we need to continue efforts to better inform and educate not only minority patients but also, broadly, communities of color. It is also incumbent on us to emphasize to dialysis and primary care providers the benefits and superior outcomes of kidney transplantation as a best practice for ESRD treatment. Still, all too often, patients come to referral for KT evaluation very late in their disease course.

For Allocation

In the case of blood group differences as a barrier to minority transplantation, we now have firm evidence that transplantation across carefully selected minor blood group incompatibility barriers is safe and can yield excellent KT graft survival. This approach has already been codified in the UNOS Kidney Allocation System and if fully adopted, is projected to result in

a sizeable increase in the rate of minority kidney transplantation. All organ procurement organizations and the centers that they serve should take full advantage of this rule immediately.

For Outcomes

APOL1 profile may have a potent influence on KT allograft outcomes after both live and deceased donation from blacks as well as on long-term black LD kidney health outcomes. On this latter point, the jury is still out regarding the long-term risk of kidney donation by blacks as a function of genetic variation at *APOL1*. Could we inadvertently be promulgating another racial disparity in health outcomes by the absence of a fuller understanding of this biology? There is a pressing need now for new organ allocation policies to be developed in lockstep with this science; these may include the recommendation to genotype specific genetic risk variants in at-risk populations as a part of donor-recipient screening protocols. In future studies, these variables, which are only now receiving attention, will need to be taken into full account in studies such as the current one from Segev and colleagues[3]: they may provide a fuller understanding of population differences and a deeper understanding of the mechanisms by which these differences affect transplant outcomes for both donors and recipients.

In conclusion, the challenge of eliminating health disparities in kidney transplantation is still a work in progress and a multifaceted one; we still have much work to do, and many questions need more in-depth exploration. Clearly, we have come a long way in addressing important rudimentary barriers to kidney transplantation. Mounting evidence that KT graft survival outcomes are narrowing between racial groups is heartening and represents a significant advance. The disparities gap in kidney transplantation, however, is not closed, and we must not be satisfied until it is.

DISCLOSURES

None.

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