CORRESPONDENCE

Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate

TO THE EDITOR: Grams et al. (Feb. 4 issue)[1] quantified the associations between "13 distinct demographic and health characteristics" and end-stage renal disease among low-risk members of seven general population cohorts in order to estimate the long-term risk of end-stage renal disease among kidney-donor candidates. Two important factors were not considered: biologic and household relatedness to a person with end-stage renal disease. Most living kidney donors are genetically related to their recipients, and heredity is a known contributor to kidney disease.[2] Furthermore, many related donors and their recipients grow up following similar dietary, exercise, and other health-related practices, factors that also affect the incidence of end-stage renal disease.[3-5] Grams et al. acknowledge the importance of genetic and environmental influences when they note that these influences may have contributed to the variation in risk associated with race uncovered in their study. The failure to incorporate these two factors into their equations renders the authors' estimates of the risk of end-stage renal disease suspect at best.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In the simulation conducted by Grams et al. to predict the risk of end-stage renal disease after kidney donation, the estimated glomerular filtration rate (eGFR) is an important variable. However, the use of the eGFR (incorporated by means of equations based on creatinine level) rather than measured GFR (incorporated by means of a reference method) is questionable. The eGFR lacks precision in the range of the GFR considered (i.e., more than 60 ml per minute per 1.73 m^2 of body-surface area).[1,2] Age is also an important variable in the calculation of the eGFR equation, and its use could introduce an association with a false positive result, especially in simulations, since age is one of the major risk factors for end-stage renal disease. Finally, in African Americans, an ancestry coefficient appears in creatinine-based eGFR equations. However, this coefficient has been criticized as being inappropriately high,[3,4] especially when applied to GFR values over 60 ml per minute per 1.73 m^2. Such an overestimation of the eGFR in African Americans could explain at least in part the higher risk observed among these patients, since their true GFR is actually lower than that calculated by means of the eGFR. Moreover, these ancestral coefficients are inaccurate in non–American-African populations.[4] For these reasons, we believe that measurement of the GFR in the evaluation of potential kidney donors to be an important, if not mandatory, step.

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THIS WEEK'S LETTERS

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No potential conflict of interest relevant to this letter was reported.

1. Delanaye P, Mariat C. The applicability of eGFR equations to different populations. Nat Rev Nephrol 2013;9:513-22.
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3. Delanaye P, Mariat C, Maillard N, Krzesinski JM, Cavalier E. Are the creatinine-based equations accurate to estimate glomerular filtration rate in African American populations? Clin J Am Soc Nephrol 2011;6:906-12.
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TO THE EDITOR: Grams et al. applied risk estimates to actual kidney donors, showing that their risk of end-stage renal disease would have been less had they not donated a kidney. Two other recent studies indicate that the relative risk of end-stage renal disease after kidney donation is increased.[1,2] A very important distinction that the Grams et al. note is the difference between relative risk and absolute risk. Since end-stage renal disease is relatively rare, a high relative risk may be equivalent to a low absolute risk if the baseline risk is sufficiently low.

In light of this consideration, we were disappointed when we attempted to use the online risk calculator. Instead of multiplying the baseline risks before donation by the known relative risks, the authors stated only that the mean absolute increase was 0.27%. We feel that absolute risk should be given. In Norway, as a consequence of our previous study on risk in kidney donors,[2] the increased risks of end-stage renal disease and death are now disclosed to all potential donors.

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No potential conflict of interest relevant to this letter was reported.

1. Muzaale AD, Massie AB, Wang MC, et al. Risk of end-stage renal disease following live kidney donation. JAMA 2014;311:579-86.
2. Mjøen G, Hallan S, Hartmann A, et al. Long-term risks for kidney donors. Kidney Int 2014;86:162-7.

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THE AUTHORS REPLY: We agree that several factors not captured in our model may affect the long-term risk of end-stage renal disease in living kidney-donor candidates. As Spital notes, these risks include heritable and environmental factors. Risks attributable to these factors have not been captured in existing studies of healthy persons. Our online tool takes full advantage of the available data. Although it should help clinicians appreciate the relationships between many predonation characteristics and the long-term risk of end-stage renal disease, the tool is in no way meant to replace a comprehensive evaluation of a donor candidate by an expert physician who carefully considers the circumstances of each individual candidate. Donor candidates with a family history of kidney disease (and in particular younger candidates with such a history) would be expected to have a higher risk of end-stage renal disease than indicated by our projection.[1] As Mjøen and Holdaas suggest, a candidate who chooses to proceed with kidney donation will face additional risk from the donation itself — including a risk of end-stage renal disease that may be at least four times as high as it would have been if the candidate had not proceeded with the donation.[2,3] Estimates of the risks of donation according to a given clinical profile are not yet available, but we agree that the development of such estimates should be a high priority for future research. We will update the online tool once estimates are available.

Delanaye and Glassock question the use of the eGFR in model development. We used the eGFR because we are unaware of any long-running cohort studies of healthy persons followed for end-stage renal disease that include measured GFR. Although there may be uncertainty with regard to the best way to incorporate age and sex in the estimation of the GFR, we are not aware of any data that support the suggestion that there is systematic misclassification according to age, race, or sex. Our model is internally consistent and calibrated to measures of observed risk in the U.S. population within the categories of age, race, and sex, irrespective of the eGFR. The question of whether a direct measurement of the GFR is necessary in all donor candidates is currently under debate,[4] but the increased risk of kidney failure among African Americans as compared with whites has also been noted among U.S. donors, in whom creatinine clearances are generally measured at the time of evaluation.[2]

Our ultimate goal is to make donor-candidate education and acceptance more empiric and defensible. Our study provides a framework for donor evaluation that is centered on the simultaneous consideration of many clinical factors relevant to the risk of end-stage renal disease, but its application requires insight and sensitivity to nuance on the part of the clinician. Suggested framing is described in detail in the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines for clinical practice.[5] We see our work as a starting point and advocate strongly for continued efforts to improve the precision and generalizability of estimates of risk before and after donation.

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Since publication of their article, the authors report no further potential conflict of interest.

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3. Mjøen G, Hallan S, Hartmann A, et al. Long-term risks for kidney donors. Kidney Int 2014;86:162-7.
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5. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guideline on the evaluation and follow-up care of living kidney donors (draft). 2015 (http://kdigo.org/home/guidelines/livingdonor/).
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Postmenopausal Osteoporosis

TO THE EDITOR: According to the results of two trials presented in Table 3 of the article by Black and Rosen (Jan. 21 issue),[1] the first 3 years of bisphosphonate use are beneficial for the prevention of fracture. However, the data presented in the table are misleading. The steep increase in the incidence of atypical fracture with prolonged bisphosphonate use is concomitant with little or no added efficacy in the prevention of fracture. On the basis of population-based data,[2] rather than theoretical calculations,[1] the risk of atypical femoral fractures for patients who receive 4 years of treatment is 126 times as high as the risk for those who did not receive treatment, which corresponds to a number needed to harm of 909 per year (odds ratio for the fifth year, 116).[2] When all available data on the efficacy of treatment for the prevention of hip fracture are considered — not just two out of all randomized, controlled trials — the number needed to treat (NNT) is 501 per year for the initial 3 years of use.[3] Because the extension of treatment beyond 5 years does not appear to prevent nonvertebral or hip fractures,[4] the NNT for a sixth year would be high — close to infinity. For the fourth and fifth years, the NNT would lie somewhere between 501 and infinity. It is uncertain whether there is a positive benefit:risk ratio when the duration of treatment is longer than 3 to 4 years. Recently suggested widening of the treatment indications[5] will increase the NNT. A consequence may be that the risks will outweigh the benefits even after treatment of shorter duration.

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Dr. Aspenberg reports receiving consulting fees from Eli Lilly and Amgen and grant support to his institution, Linköping University, from Eli Lilly and Amgen; holding stock in AddBIO, a company trying to commercialize a method for applying a bisphosphonate coating to implants to be inserted in bone; and holding a patent for this method. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Black and Rosen suggest that the discontinuation of bisphosphonates after 5 years