issues in the neonate, which makes very clearly the argument that a decision to treat a neonate differently from an older child is unjustified.[8]

Finally, and most importantly, van Stralen *et al.* provide outcome data over the first 5 years of life.[4] However, the data have to be viewed in the context that we do not know their completeness. It is likely not only that the sickest children have been excluded, but also that others with equally poor renal function may not have been included because of purposeful delay in initiating dialysis. The importance of this is that the missing data will influence the survival and causes of death in the cohorts that have been treated. However, that said, the large numbers are likely to override these difficulties. The survival figures are impressive. Figure 1 illustrates the percentage survival up to 5 years of age of both the data of van Stralen *et al.*[4] and data on 193 neonates and 505 children aged 1–24 months starting chronic dialysis in the United States during a slightly earlier era (1992–2005).[2] Survival until 2 years of age seems very similar, but thereafter there is a suggestion that survival in the current study by van Stralen *et al.* may be superior to that of both the neonates and the under-2-year-olds in the United States. That 22% of the children have renal transplants is also encouraging. However, despite the suggestion that survival is improving, the incidences of growth retardation (63%), anemia (55%), and hypertension (76%) at 2 years are disappointing.[4] All three of these factors are well known to affect long-term outcome. All can be successfully managed with careful attention to detail. We owe this to these youngest children, who have the greatest potential life expectancy of all our patients.

DISCLOSURE
The author declared no competing interests.

REFERENCES

1. Zurowska AM, Fischbach M, Watson AR *et al.* Clinical practice recommendations for the care of infants with stage 5 chronic kidney disease (CKD5). *Pediatr Nephrol* 2013; **28**: 1739–1748.
2. Carey WA, Talley LI, Sehring SA *et al.* Outcomes of dialysis initiated during the neonatal period for treatment of end-stage renal disease: a North American Pediatric Renal Trials and Collaborative Studies special analysis. *Pediatrics* 2007; **119**: e468–e473.
3. Mekhali D, Shaw V, Ledermann SE *et al.* Long-term outcome of infants with severe chronic kidney disease. *Clin J Am Soc Nephrol* 2010; **5**: 10–17.
4. van Stralen KJ, Borzych-Dużalka D, Hataya H *et al.* Survival and clinical outcomes of children starting renal replacement therapy in the neonatal period. *Kidney Int* 2014; **86**: 168–174.
5. Hogan J, Dourthe ME, Blondiaux E *et al.* Renal outcome in children with antenatal diagnosis of severe CAKUT. *Pediatr Nephrol* 2012; **27**: 497–502.
6. Teh JC, Frieling ML, Sienna JL *et al.* Attitudes of care givers to management of end-stage renal disease in infants. *Perit Dial Int* 2011; **31**: 459–465.
7. Rees L. Infant dialysis. What makes it special? *Nat Rev Nephrol* 2013; **9**: 15–17.
8. Lantos JD, Warady BA. The evolving ethics of infant dialysis. *Pediatr Nephrol* 2013; **28**: 1943–1947.

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End-stage renal disease in living kidney donors

Neil Boudville[1] and Amit X. Garg[2,3]

The paper by Mjøen *et al.* raises important concerns about the long-term consequences of living donation, including a long-term increased risk of end-stage renal disease after an individual undergoes donor nephrectomy. These potential risks need to be communicated to future living kidney donors and should be an impetus for ongoing investigation.

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More than 27,000 living kidney donations are performed worldwide each year.[1] In certain countries it is the only financially viable treatment option for most patients with kidney failure. The practice, however, is predicated on the assumption that the advantages to the recipient, society, and the donor (for instance, psychological benefit) outweigh any harms (or risk of harm) to the donor. The perioperative (<90 days) outcomes of donor nephrectomy are well documented, including a perioperative mortality rate of 0.03% and a complication rate of 5–15%. Adverse psychological outcomes in donors, including those related to poor recipient outcomes, are uncommon.[2]

The long-term medical risks following living kidney donation remain an area of study. Ibrahim *et al.*'s findings from Minnesota were reassuring: approximately 3700 donors had a similar survival and a lower estimated incidence of end-stage renal disease (ESRD) compared with non-donors selected from population surveys.[3] A Canadian study also demonstrated no increased mortality or major cardiovascular events in approximately 2000 living kidney donors compared with 20,000 matched non-donors, with no separation of the survival curves (follow-up was a median of 6.5 years, with a maximum of 17.7 years).[4]

Mjøen *et al.*[5] (this issue) now describe the long-term outcomes of 1901 living kidney donors in Norway. Such data are welcome, and Mjøen and colleagues should be congratulated for undertaking this study. A major

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advantage of this study is the comprehensive nature of the data, with all kidney transplantations in Norway being performed within one center. In addition, few Norwegian nationals emigrate, ensuring a high rate of follow-up through national registries, though we presume the emigration rate is unlikely to have been zero (as the authors report). These characteristics enabled the authors to obtain a longer follow-up than most prior studies on living donors. The authors also accessed another Norwegian population-based sample to generate a matched non-donor comparison group.

This paper demonstrates that living donors have poorer survival compared with matched non-donor controls, with the difference apparent only after 10 years of follow-up (there were 224 deaths in the living donor group). The hazard ratio for all-cause mortality in living donors compared with controls was 1.3, in the fully adjusted model (95% confidence interval 1.1–1.5), and the hazard ratio for cardiovascular death was similar. More details about event rates to better understand absolute risks would have been useful to enhance our understanding of these results.

The paper also demonstrates an approximately 11-fold increase in the hazard ratio for ESRD in donors compared with matched non-donor controls (95% confidence interval 4.4–29.6), with 9 donors developing ESRD. All such donors were genetically related to the recipient, and the etiology of kidney failure appeared predominantly immunological.

The commencement of observation of the living donor cohort was different from that of the non-donor controls: 1963–2007 for the living donors and 1984–1987 for the non-donor controls. In the baseline table it would have been useful to see the year of cohort entry (in categories) to better appreciate this difference between donors and non-donor controls. The difference in year of cohort entry between the two groups has two implications: (1) Secular changes in individuals' health and their health care mean that the two groups are not fully comparable at baseline and follow-up, and these between-group differences that impact outcome may not be fully accounted for in 'adjusted' analyses that consider inclusion year. (2) The longer duration of follow-up in donors (maximum follow-up 43.9 years) compared with non-donors (maximum follow-up 24.9 years) may also result in a higher incidence of ESRD in donors if the incidence is not constant over time and increases with the duration of follow-up. (For example, there is some relationship between the duration of follow-up and the risk of ESRD that requires clarification. The authors note a significant inverse association between inclusion year and ESRD risk; however, they also indicate that the proportional hazards assumption was not violated.)

There are other limitations to this study, including the lack of measurement of kidney function or proteinuria in the control group at baseline, and the lack of such measurements in both groups during follow-up. Adjustment may not fully account for differences between the two groups in baseline age, which was higher in donors than in non-donor controls. Acceptance of living kidney donors with an estimated glomerular filtration rate as low as 70 ml/min/1.73 m^2—compared with 80 ml/min/1.73 m^2, which is an accepted lower threshold for most units—may also lead to worse outcomes in the donor group than would be seen in other centers. Finally, with only 31 ESRD events, there may be some concerns about model overfitting, particularly with multiple adjusters.

This all being said, an increased incidence rate of ESRD in donors compared with non-donor controls is now also corroborated in a recently presented abstract on almost 100,000 living kidney donors from the United States.[6] In that study, the incidence rate of ESRD was eightfold higher in donors (comparable to the 11-fold increase in the incidence rate in this Norwegian study). Thus, there are now at least two studies describing an approximately tenfold increase in the incidence of ESRD after donation, which is a serious concern.

The findings from these two studies are very important and should influence the information we provide to potential donors. In terms that patients may easily understand, we can state that if we follow 10,000 donors for 20 years (with the assumption all survive 20 years), 60 will develop ESRD (which approximates 302 in 1,000,000 person-years as in the Mjøen *et al.* study[5]). In many nations the average life expectancy is now 90 for women, and 85 for men. Thus, many donors may live 40, 60, or more years with one kidney. Rough lifetime estimates of ESRD (assuming a constant incidence over time, which may not be the case) would then be as noted in Figure 1.

These findings may impact our criteria for donor selection. We will likely want a higher level of pre-donation kidney function (estimated glomerular filtration rate >90 ml/min/1.73 m^2) for younger individuals who are expected to live 50 or more years with one kidney (recognizing we do not have ideal evidence to inform what is the optimal acceptance threshold). The importance of excellent health behaviors, both before and after donation,

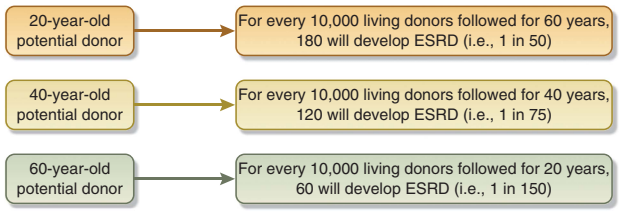

Figure 1 | Estimating the risk of developing end-stage renal disease (ESRD) for potential living kidney donors during their expected lifespan as part of the informed consent process. Uses an incidence rate of 300 per 1,000,000 person-years (which approximates the incidence rate noted by Mjøen *et al.*[5]). Assumptions: (1) Incidence is constant as someone ages and with duration after donation (which it may not be). (2) All donors live to the age of 80 (that is, with no censoring for death or other reasons prior to this time).

should continue to be emphasized. This should include an annual serum creatinine, urine protein, and blood pressure measurement in follow-up.

Despite this lack of consistent evidence on the long-term outcomes of living kidney donation, fueled by the increasing demands for organs, there has been a growing trend worldwide to accept donors with features that historically would have precluded donation.[7] If indeed living kidney donation does lead to some adverse outcomes, accepting donors with additional comorbidities (such as obesity, hypertension, and impaired glucose tolerance) may accentuate these poor outcomes. However, the practice of accepting donors with extended criteria may continue to be reasonable—but defensible only if there are ongoing detailed efforts to better understand the long-term outcomes, so practice can be corrected if donor harm over many decades is greater than initially anticipated.

Finally, we need better information on the incidence of a very low estimated glomerular filtration rate prior to ESRD in kidney donors. This is expected to be an order of magnitude higher than the incidence of a need for dialysis or a kidney transplant and may be an important source of patient morbidity. Rather than registries, such data would be best obtained through a long-term prospective cohort study with a comparable group of non-donor controls.

DISCLOSURE
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REFERENCES

1. Horvat LD, Shariff SZ, Garg AX. Global trends in the rates of living kidney donation. *Kidney Int* 2009; **75**: 1088–1098.
2. Gross CR, Messersmith EE, Hong BA *et al.* Health-related quality of life in kidney donors from the last five decades: results from the RELIVE study. *Am J Transplant* 2013; **13**: 2924–2934.
3. Ibrahim HN, Foley R, Tan L *et al.* Long-term consequences of kidney donation. *N Engl J Med* 2009; **360**: 459–469.
4. Garg AX, Meirambayeva A, Huang A *et al.* Cardiovascular disease in kidney donors: matched cohort study. *BMJ* 2012; **344**: e1203. doi:10.1136/bmj.e1203.
5. Mjøen G, Hallan S, Hartmann A *et al.* Long-term risks for kidney donors. *Kidney Int* 2014; **86**: 162–167.
6. Muzaale A, Massie A, Wainright J *et al.* Risk of end-stage renal disease following live kidney donation. *JAMA* 2014; **311**: 579–586.
7. Taler SJ, Messersmith EE, Leichtman AB *et al.* Demographic, metabolic, and blood pressure characteristics of living kidney donors spanning five decades. *Am J Transplant* 2013; **13**: 390–398.