for adjusted association with immunosuppressants in subsequent regression models. Therefore, Dr. Mange can be reassured that our results are not influenced by the multiple estimates of GFR per patient.

Second, Dr. Mange suggests that creatinine measurements may be differentially missing between patients who received different immunosuppressants. Nonrandom missing data could introduce bias if the annualized change in GFR differed in patients with and without missing creatinine measurements. All study patients had three creatinine measurements recorded in the first two post-transplant years, and over 80% of all creatinine measurements were available during follow-up. There was no association between missing creatinine values and transplant year or type of immunosuppression; therefore, bias caused by nonrandom missing values is very unlikely.

Third, Dr. Mange suggests bias caused by differences in the methods used to measure creatinine between transplant centers. In order for this to affect our results, the creatinine assays in centers using tacrolimus (or mycophenolate) would have to systematically differ from centers using cyclosporine (or azathioprine)—which seems very improbable. Nonetheless, because most patients would have creatinine measurements in the same center, the annualized change in GFR in individual patients would not be affected by differences in assays between centers.

As discussed in our manuscript, we agree that readers must consider a variety of limitations inherent to analyses of large databases. However, we do not believe that particular issues raised in this letter are relevant to our analysis.

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Development of malignancy after treatment of idiopathic membranous nephropathy

To the Editor: With great interest, we have read the paper in a recent issue of *Kidney International* by Keiichi Yoshimoto et al [1] that pathologic findings of initial biopsies reflect the outcomes of membranous nephropathy (MN). In this study, seven patients ($7/105 \times 100\% = 6.66\%$) eventually died of malignancies (gastric cancer 3, pancreatic cancer 1, lung cancer 1, laryngeal cancer 1, leukemia 1). Although they were diagnosed initially as idiopathic membranous nephropathy, we wondered whether the malignancy was the underlying cause of MN or the complication of long-term immunosuppressive therapy (e.g., cyclophosphamide). MN had been reported to be associated with neoplasms, and some patients with malignancies had been documented presenting with nephrotic-range proteinuria. In David's study [2], nine of 87 ($9/87 \times 100\% = 10.3\%$) "idiopathic" MN patients were associated with malignancy. Hence, a search for malignancy is warranted in all adult patients presenting with MN. Pathologically, deposits at sites other than the subepithelial aspect of the glomerular basement membrane (GBM) favor the presence of secondary forms of MN. We would like to know if any deposits were identified at mesangial, subendothelial, tubular basement membrane, interstitial, or vessel area in these seven malignant patients. We would also like to know whether there was any difference in the pathologic findings (according to Yoshimoto's classification) between the seven malignant patients and those without malignancies. On the other hand, the possible carcinogenic effect of long-term immunosuppressive therapy should be also considered because the carcinogenic potency of alkylating agents had been reported in the literature [3].

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Reply from the authors

We would like to thank you for the interest to our article [1]. We agree with the comments that a search for malignancy is warranted in all adult patients with membranous nephropathy; therefore, we routinely examined them by chest x-ray, upper gastrointestinal endoscopic study, abdominal ultrasonography, or computed tomography, and stool occult blood (if positive, lower gastrointestinal endoscopic study). Seven patients died with malignancy in our study, but malignancy was not detected in all of them at first as described [1].

Three of seven patients were treated with corticosteroid and cyclophosphamide, one patient with gamma globulin and cyclophosphamide, two patients with corti-