Letter to the Editor

Estimating the Prevalence of Low Glomerular Filtration Rate Requires Attention to the Creatinine Assay Calibration

To the Editor: In the May issue of *JASN*, Clase *et al.* (1) report a much higher estimate of the prevalence of low glomerular filtration rate (GFR) than recently published in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines, "Chronic Kidney Disease: Evaluation, Classification and Stratification" (2). The authors also conclude that "laboratory-generated clearance reports cannot be recommended without further study." We disagree with this conclusion and the calculations upon which it is based.

Recently published data indicate that serum creatinine assays on the same samples were 0.23 mg/dl higher in the Third National Health and Nutrition Examination Survey (NHANES III) than in the Modification of Diet in Renal Disease (MDRD) study (3). The K/DOQI report calculates the prevalence of moderately (30 to 60 ml/min per 1.73m^2) or severely (15 to 29 ml/min per 1.73m^2) decreased GFR at 4.3% and 0.2%, respectively, among adults age 20 yr and older in the United States. This estimate is based on the NHANES III study after accounting for calibration differences between NHANES III and MDRD study laboratories. Interestingly, Clase *et al.* derive very similar estimates (4% and 0.17%) for nondiabetic black and white adult Americans under the hypothetical statement "if NHANES III–measured creatinine were systematically as much as 0.2 mg/dl (17.7 μmol/L) higher than MDRD-measured creatinine." These estimates are markedly lower than the comparable estimates reported in their abstract and main results of 13% below 60 ml/min per 1.73m^2 and 0.26% below 30 ml/min per 1.73m^2. The latter estimates reflect methodologic bias, not the underlying GFR.

Calibration explains the "unexpected" nature of the authors' findings; therefore, we do not think the data provide any evidence against the appropriate use of equations to estimate GFR. In fact, estimated GFR in NHANES III is generally similar to studies of inulin clearance in normal volunteers (see Figure 9 of K/DOQI report [2]). We agree with the authors that biased creatinine results similar to those from the NHANES III reference laboratory would be obtained by at least some clinical laboratories. However, we strongly disagree with their conclusion that it is premature for laboratories to report a calculated clearance estimate with each creatinine measurement. Serum creatinine is widely used to detect and follow the progression of kidney disease; therefore, the relevant question is whether reporting an estimated GFR would provide an improvement over current practice. We believe laboratory reporting of estimated GFR should be implemented for three main reasons: (*1*) estimated GFR provides a better estimate of GFR than serum creatinine; (*2*) estimated GFR is more readily interpretable than serum creatinine by both patients and physicians; and (*3*) calibration differences in serum creatinine measurements are more readily detected when estimated GFR is reported because GFR estimates account for differences in patients' age and gender. It is our hope that as laboratories implement the calculation, they will also implement corrections for their own serum creatinine calibration. Initial progress in this regard is encouraging, with one major HMO moving in this direction and an NIH-organized workshop on standardization of the serum creatinine assay scheduled for this summer.

An estimated GFR cutoff of less than 60 ml/min per 1.73m^2 for diagnosing CKD in the absence of kidney damage was chosen by the K/DOQI Work Group, with interlaboratory variation in measurement of serum creatinine in mind. The Work Group recommended caution in interpreting GFR estimates of 60 to 90 ml/min per 1.73m^2 as low, especially in the elderly. The advantage of estimating GFR over reporting serum creatinine can be illustrated by the following example. A serum creatinine of 1.4 mg/dl corresponds to an estimated GFR of 40 ml/min per 1.73m^2 in a 70-yr-old white woman. This translates to moderate (Stage 3) chronic kidney disease and a higher prevalence of anemia and other co-morbidities. If serum creatinine measurements from a laboratory that overestimates serum creatinine by 0.23 mg/dl is used, the estimated GFR would be 49 ml/min per 1.73m^2. On the other hand, for a 40-yr-old African-American man, a serum creatinine of 1.4 mg/dl corresponds to an estimated GFR of 72 (89 in a lab calibrated high) ml/min per 1.73m^2. As expected, calibration takes on a greater importance at higher GFR and when individuals are close to a given GFR cutoff (3). However, in our opinion, physicians are much better equipped to make good decisions when provided with an estimated GFR in addition to the serum creatinine on laboratory printouts.

We would like to emphasize that the belief that 24-h urine is a better solution than estimating GFR from serum creatinine is not supported by most published data (2). For example, in the African-American Study of Kidney Disease and Hypertension (4), the median absolute value of percent difference from iothalamate GFR was 23% for 24-h creatinine clearance compared with 12% for the estimates from the MDRD study equation. This result was based on 1703 study screenees with a mean (SD) GFR of 57 (23) ml/min per 1.73m^2 (R^2 = 0.59 and 0.82, respectively). Errors in urine collection are frequent, and urinary creatinine clearance suffers similar sensitivity to assay calibration as equations because non-creatinine chromogens are present in serum but not urine. Reliance on a cancellation of serum non-creatinine chromogens with creatinine secretion has no scientific basis and may have led to the high interlaboratory variation in creatinine calibration. In our opinion, it is time to do away with routine 24-h urine collections to

estimate creatinine clearance and to adopt estimation of GFR from standardized serum creatinine measurements. The recently published clinical practice guidelines (2) provide the rationale for standardized diagnosis and classification of chronic kidney disease, which considers early detection and treatment of complications of decreased GFR, including hypertension and other cardiovascular disease risk factors, as well as strategies to slow the progression of kidney disease. The evidence for specific interventions should be rigorously evaluated, but a number of recommendations already exist for this high-risk patient population. Efforts to improve the prediction and search for better markers are useful. The sooner this is done, the better care patients with kidney disease will receive.

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Reply from the Authors: We thank Coresh *et al.* for their comments. We provided NHANES III population estimates for four common methods of glomerular filtration rate (GFR) assessment: the Modification of Diet in Renal Disease (MDRD), Cockcroft-Gault, Couchoud, and reciprocal of creatinine methods (1). On the basis of the prevalence of low GFR and the consequent potential for laboratory-based reporting of calculated GFR to increase nephrology referrals by an order of magnitude, we recommended against implementation of this strategy before further evaluation. Since we wrote the article, the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines (2) have appeared; these guidelines recommend immediate implementation of GFR-based laboratory reports.

The first issue concerns the prevalence of low GFR. As Coresh *et al.* point out, differences between the NHANES III MDRD GFR prevalence estimates that we provide and those recently published as part of the K/DOQI guidelines (2) are largely due to the inclusion in the K/DOQI analyses of a correction factor to account for differences in calibration between the White Sands Research Center laboratory (used in NHANES III) and the Cleveland Clinic laboratory. The Cleveland Clinic laboratory was used in the MDRD study; data from these participants were used to derive and validate the MDRD equations for calculation of GFR and to validate the Cockcroft-Gault formula (3). The calibration difference was recently reported by Coresh *et al.* (4): creatinine measured at the White Sands laboratory is 0.23 mg/dl (20.3 μmol/L) higher than that measured at the Cleveland Clinic. This information was not available in the public domain at the time of our report. We followed the procedures of the analytic guidelines for NHANES III (5). Previous reports of renal function based on creatinine from the NHANES III data set have not included recalibration to an external standard (6).

The use of a correction factor in all the K/DOQI analyses is reported in Appendix 2 (2), but is not, to our knowledge, found in the text and tables of the document. It may not be readily apparent that all K/DOQI analyses are adjusted in this way; for example, in a recent editorial (7), the reason for the difference between our results and the K/DOQI tables was questioned and the question was unanswered. In our article, as noted by Coresh *et al.*, we reported that a calibration difference of the order of 0.2 mg/dl would have a large effect on the prevalence of low GFR, particularly at higher levels of GFR. Using the actual calibration difference, Coresh *et al.* have recently documented the same issue (4). To highlight this issue and to document the magnitude of the effects that are introduced by inter-laboratory differences in serum creatinine measurements, we present the prevalence of low MDRD GFR in US adults without diabetes (the study population we reported) using the newly published calibration factor. The overall prevalence of MDRD GFR less than 30 ml/min per 1.73 m^2 was 0.16%, for GFR 30 to 59 ml/min per 1.73 m^2 was 3.2%, and for GFR 60 to 79 ml/min per 1.73 m^2 was 14.5% (Figure 1). For reference, we have also duplicated the race-gender stratified analyses using the MDRD formula applied to adjusted creatinine (Figure 2). The largest validation series for the Cockcroft-Gault formula also derived from creatinine measured at the Cleveland Clinic laboratory as part of the MDRD study; therefore, one could argue that Cockcroft-Gault estimates from NHANES III should also be recalibrated to the Cleveland Clinic laboratory.

In their letter, Coresh *et al.* argue that the calibration issue explains the unexpected nature of our findings. We do not agree. We discussed the calibration issue in our original paper. Even accounting for differences in inter-laboratory variation, we feel that the adjusted prevalence of low GFR is surprisingly high, particularly in the elderly. For example, our adjusted estimate for the prevalence of GFR between 30 and 60 ml/min per 1.73 m^2 (stage 3 disease by the K/DOQI classification [2]) in nondiabetic Americans is 3.2%. The K/DOQI adjusted estimate for GFR 30 to 60 ml/min per 1.73 m^2 in the total US
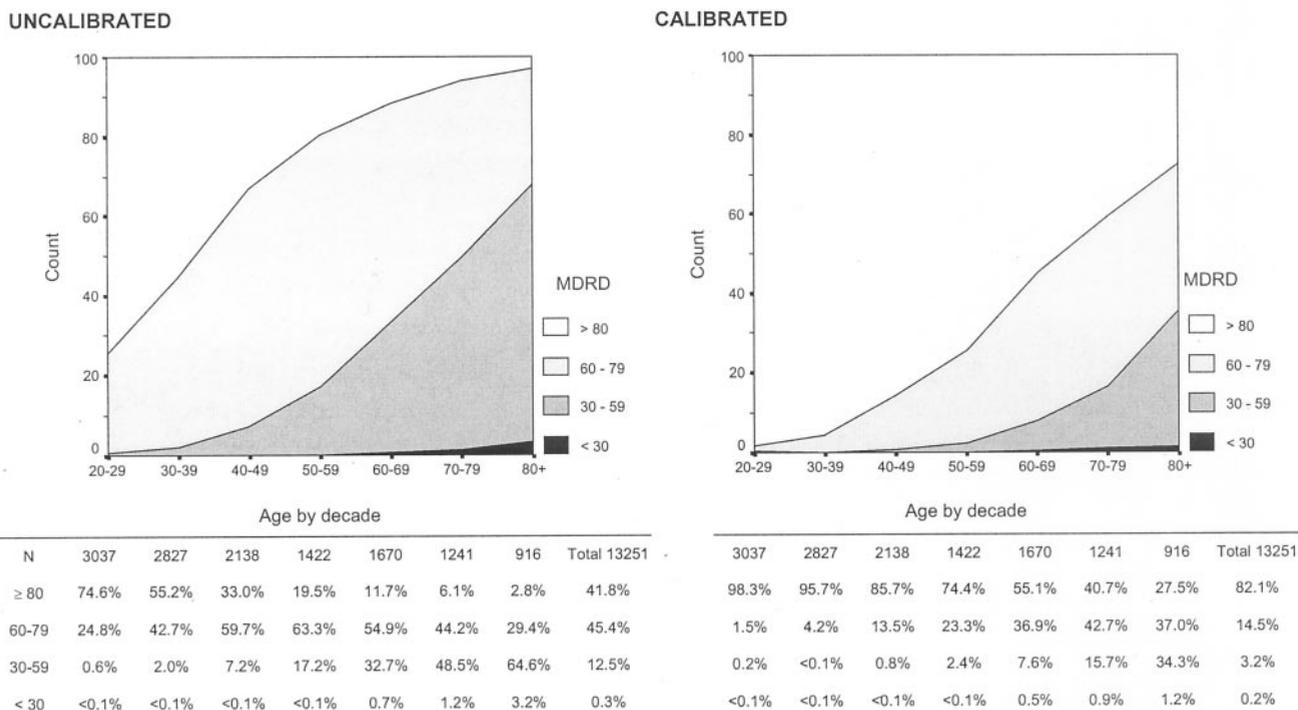
UNCALIBRATED

N	3037	2827	2138	1422	1670	1241	916	Total 13251
≥ 80	74.6%	55.2%	33.0%	19.5%	11.7%	6.1%	2.8%	41.8%
60-79	24.8%	42.7%	59.7%	63.3%	54.9%	44.2%	29.4%	45.4%
30-59	0.6%	2.0%	7.2%	17.2%	32.7%	48.5%	64.6%	12.5%
< 30	<0.1%	<0.1%	<0.1%	<0.1%	0.7%	1.2%	3.2%	0.3%

CALIBRATED

3037	2827	2138	1422	1670	1241	916	Total 13251
98.3%	95.7%	85.7%	74.4%	55.1%	40.7%	27.5%	82.1%
1.5%	4.2%	13.5%	23.3%	36.9%	42.7%	37.0%	14.5%
0.2%	<0.1%	0.8%	2.4%	7.6%	15.7%	34.3%	3.2%
<0.1%	<0.1%	<0.1%	<0.1%	0.5%	0.9%	1.2%	0.2%

Figure 1. Nondiabetic adults in NHANES III. Weighted distribution of the level of predicted GFR (MDRD categories) in ml/min per 1.73 m^2, by age (in decades), for the total US nondiabetic black and white adult population. Uncalibrated estimates are calculated from serum creatinine as reported in NHANES III database; calibrated estimates are calculated after subtraction of 0.23 mg/dl (20.3 μmol/L) from serum creatinine to account for differences between the White Sands and the Cleveland Clinic laboratories. Methods are otherwise as described in our original publication.

population is 4.3%. Among the nondiabetic elderly, 8% of people in their sixties, 16% of people in the seventies, and 34% of people in their eighties (Figure 2), have GFR in this range and, if their values were confirmed on repeat testing, would be classified as having stage 3 chronic kidney disease according to K/DOQI guidelines. We argue that our finding of a high prevalence of GFR between 30 and 60 ml/min per 1.73 m^2 (of the same order of magnitude as diabetes mellitus, which has been estimated at 5.1% of the population [8]) should lead the nephrology community to question whether a test result in this range is invariably indicative of disease. On the basis of current evidence, we believe that GFR ranging from 30 to 60 ml/min per 1.73 m^2 at a population level might be better conceptualized as a probable risk factor. A thoughtful discussion of the issues that surround the classification of clinical findings as diseases or as risk factors is found in a recent article by Moynihan *et al.* (9). This issue of terminology applies also to the criteria used to define stage 1 and 2 chronic kidney disease in the K/DOQI classification (a further 3.3% and 3.0% of the population, respectively, according to K/DOQI estimates [2]).

The second issue concerns the evidence base surrounding the recommendation for widespread laboratory reporting of GFR. We do not disagree that equation-based estimates are the preferred method of estimating GFR (we wrote, "they represent the best available option for the estimation of clearance in large studies" in the Discussion section of our article [1]) and

have nowhere suggested that creatinine clearances based on 24-h urine collection are preferable.

GFR is a familiar and helpful concept to nephrologists. However, most healthcare workers who review creatinine data are not nephrologists. Most of the impact of the proposed change will be on professionals who are experienced in the interpretation of serum creatinine but inexperienced in the interpretation of GFR or clearance data. This will result in identification of many people with low GFR who would not previously have been recognized, particularly in the elderly. The rationale behind recommendations for laboratory reporting of GFR is that these patients will benefit from having been recognized, and that ultimately this recognition would lead to reduction in the burden of end-stage renal disease (ESRD). This is an important and testable hypothesis, not a proven strategy. We wish to express our concern that this untried intervention will be implemented before evaluation of its consequences, not all of which will be positive. Implementation of a new strategy on this scale mandates careful consideration of the risk-benefit ratio and of cost-effectiveness. The benefits of specific diagnosis and management in people who are currently not referred to nephrologists have not been studied. Relevant data suggesting that benefits may be more limited in unreferred than in referred populations include the following.

1. Referred populations would be expected to differ substantially from unreferred populations, and there are emerging
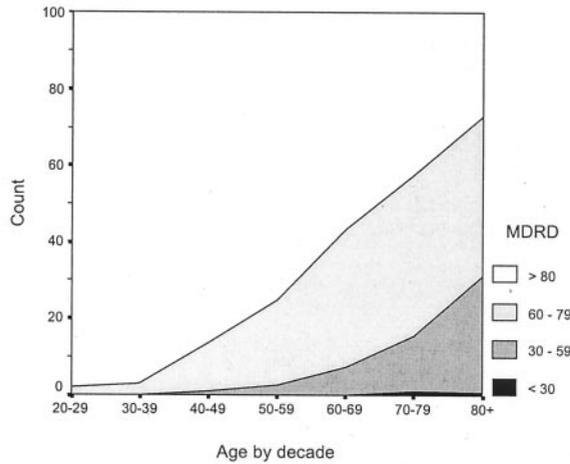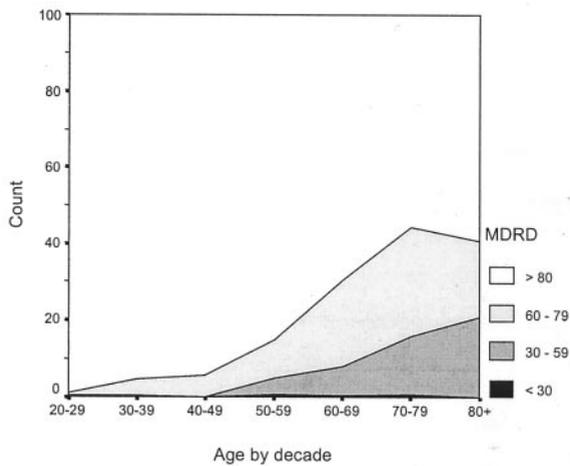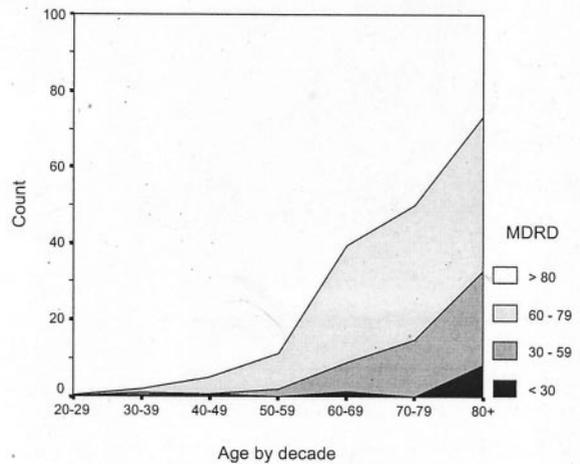
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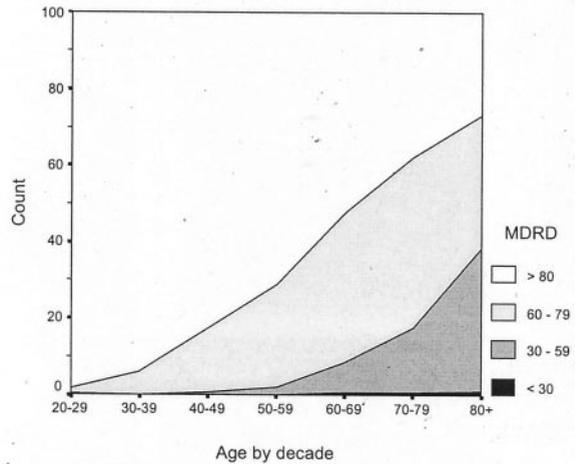
N	970	823	708	490	657	470	404	Total 4522
≥ 80	98.1%	97.0%	86.5%	75.0%	56.6%	42.5%	27.2%	83.6%
60-79	1.9%	3.0%	12.5%	22.5%	36.0%	41.8%	41.7%	13.5%
30-59	0%	0%	1.0%	2.5%	7.4%	14.6%	30.5%	2.8%
< 30	0%	0%	0%	0%	0%	1.1%	0.6%	0.1%

WHITE WOMEN

1028	999	724	568	616	539	435	Total 4909
98.2%	94.1%	82.8%	71.3%	52.3%	37.9%	26.7%	78.5%
1.4%	5.9%	16.6%	26.7%	39.1%	44.7%	34.8%	17.4%
0.3%	<0.1%	0.6%	2.1%	7.8%	16.6%	37.5%	4.0%
0%	<0.1%	0%	0%	0.8%	0.8%	1.1%	0.2%

BLACK MEN

N	455	435	314	162	209	128	32	Total 1735
≥80	99.0%	95.4%	94.3%	85.0%	69.6%	55.5%	59.4%	91.2%
60-79	0.7%	4.1%	5.5%	10.1%	22.6%	28.7%	19.7%	6.6%
30-59	0.2%	0.2%	0.1%	4.3%	7.4%	15.4%	20.9%	2.0%
< 30	0%	0.2%	0%	0.7%	0.4%	0.5%	0%	0.2%

BLACK WOMEN

584	570	392	202	188	104	45	Total 2085
99.7%	98.0%	95.1%	88.7%	60.8%	50.0%	26.8%	91.0%
0.2%	1.1%	4.2%	9.2%	30.2%	35.2%	40.3%	6.5%
0%	0.5%	0.1%	2.1%	7.7%	14.7%	24.6%	2.0%
0.1%	0.4%	0.5%	0%	1.4%	0%	8.3%	0.5%

Figure 2. Nondiabetic adults in NHANES III. Weighted distribution of level of predicted GFR (MDRD categories) in ml/min per 1.73 m^2, by age (in decades), stratified by race and gender and calibrated to the Cleveland Clinic laboratory by subtraction of 0.23 mg/dl (20.3 μmol/L) from serum creatinine. Methods are otherwise as described in our original publication.

data to support this hypothesis. Proteinuria is a potent and consistent multivariable predictor of risk of progression of renal insufficiency. In the MDRD study A (GFR 25 to 55 ml/min per 1.73 m^2), 27% of patients had greater than 1000 mg/d proteinuria (10). In contrast, in NHANES III, only 3.3% of participants with a GFR between 30 and 60 ml/min

per 1.73 m^2 demonstrated greater than 288 mg/day of albuminuria (approximated from Couchoud serum creatinine cut-points and random urine albumin-to-creatinine ratio respectively) (11). While the prognostic significance of low GFR in unreferred populations is unknown, on the basis of proteinuria we would expect overall that unreferred low

GFR is less of a risk for ESRD than is low GFR in patients seen and studied by nephrologists.

2. The rate of loss of GFR in unreferred populations with low GFR has not, to our knowledge, been reported.

3. Benefits of therapy to reduce the rate of progression of renal insufficiency have been tested only in referred populations.

4. Studies of optimal approaches to the diagnosis of the etiology of renal insufficiency are lacking even for referred populations. Part 9 of the K/DOQI guidelines outlines key clinical considerations and possible diagnostic tests, but cautions that "many of the recommendations in this section have not been adequately studied and therefore represent the opinion of members of the Work Group" (2). The current state of knowledge does not permit the publication of evidence-based diagnostic pathways that could be implemented in a primary care setting.

Potential adverse effects of the proposed intervention (including calculated GFR with all creatinine reports) include the following.

5. Labeling effects. Diagnosis and referral for evaluation of hypertension were shown to be associated with subsequent reductions in income and increases in absenteeism up to 5 yr after screening (12). Effects on anxiety levels and social functioning by labeling people with a diagnosis of low GFR might also be anticipated. These factors are particularly important in the light of the K/DOQI recommendation that patient and public education programs be developed encouraging the philosophy "Know your number!" (2).

6. Overlabeling due to inter-laboratory variation of serum creatinine is a potential problem. The College of American Pathologists reported that in laboratories surveyed in 1994, creatinine was overestimated on average by 13 to 17% (0.12 to 0.17 mg/dl; 11 to 15 μmol/L) (13). As we reported in our original article, when creatinine is converted into GFR, a difference of this order of magnitude has a large impact on the prevalence of disease. In NHANES III, the prevalence of GFR 30 to 60 ml/min per 1.73 m^2 is increased fourfold (12.5% *versus* 3.2%) when the calibration factor is not used for creatinine measured at the White Sands laboratory (Figure 1).

7. Increased investigation. Most suggested investigations for the etiology of chronic renal insufficiency are noninvasive, but some, including renal biopsy and angiography, carry a risk of harm. Harm associated with screening strategies that are superficially noninvasive is well documented in other contexts (14,15). Increased investigation will also increase the costs of care. To our knowledge, no estimates of the cost-effectiveness of any investigational strategy for low GFR/CRI are available.

8. Increased referral to nephrologists. In addition to the general issue of increasing healthcare utilization, increased referral poses a specific challenge to a limited societal resource. The continuing and projected growth of ESRD implies that this resource will be severely taxed over the next decade, and it is unclear whether the training of adequate numbers of new nephrologists to account for this

expansion will be feasible (16). The Ad Hoc Working Committee estimated that there were about 5000 nephrologists in practice in the United States in 1997 (16). Given the prevalence of MDRD GFR 30 to 60 ml/min in the population (around 4%; 7.6 million Americans by corrected estimates [2]), the potential for increased workload is immense should the proportion of those with GFR in this category who are referred suddenly increase. This would also negatively impact the care of the more selected group of patients who are currently referred and of those with ESRD.

We share the concerns about the limitations of serum creatinine expressed by your correspondents and summarized in detail in the K/DOQI guidelines. We also agree that strategies are urgently required to reduce the societal burden of ESRD. Reporting GFR (if this is implemented in conjunction with appropriate calibration to a gold standard) is a potential strategy to this end; our point of disagreement is whether the available data are sufficiently strong that this should be broadly implemented now without further evaluation. We argue that the current state of knowledge of the community epidemiology of renal disease is such that scarce resources would be better devoted to further research into appropriate methods of detection, diagnosis, and treatment of those most at risk for progressive chronic renal insufficiency and ESRD.

Yours sincerely,

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