In 2002, the Kidney Disease Outcomes Quality Initiative recommended the use of an estimated glomerular filtration rate (eGFR) to detect early kidney disease (1). Subsequently, the National Kidney Disease Education Program (NKDEP) has taken the lead in promoting the use of eGFR. In their recommendations to health professionals (2), the NKDEP suggested determining an eGFR, as well as measuring a spot urine albumin/creatinine ratio, in patients at high risk for kidney disease, i.e., those with diabetes, hypertension, or a family history of kidney disease. The NKDEP defines chronic kidney disease (CKD) as a GFR persistently $\leq 60$ mL $\cdot$ min $^{-1} \cdot 1.73$ m$^2$ or albuminuria $>30$ mg/g creatinine. For calculating eGFR in adults, the NKDEP recommends using either of 2 versions of the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.

In their "Suggestions for Laboratories," the NKDEP "strongly encourages clinical laboratories to automatically report eGFR when serum creatinine is reported" (3). Beginning in late 2003, members of various kidney societies were asked to strongly encourage their local laboratories to report an eGFR with each creatinine result. Recently, this encouragement has extended to the proposal in several states of laws requiring the reporting of eGFR with every creatinine measurement. As might be expected, the performance of the prediction equation degrades when it is applied to populations other than CKD patients or when creatinine is measured by other methods.

The original MDRD Study equation was developed and validated in populations of CKD patients and is based on creatinine concentrations measured with a kinetic alkaline picrate method that is no longer in use (5). The performance of the prediction equation degrades when it is applied to populations other than CKD patients or when creatinine is measured by other methods.

The NKDEP Laboratory Working Group (LWG) has recently described the problems associated with interlaboratory differences in creatinine measurements, including calibration differences and variable interference by noncreatinine chromogens (6). Variability in creatinine measurements can considerably impair the accuracy of any mathematical prediction of GFR, including the MDRD Study equations, when applied globally without regard to creatinine method and with a single, universal decision value of $<60$ mL $\cdot$ min $^{-1} \cdot 1.73$ m$^2$.

The LWG has recommended a process that could lead to harmonization of creatinine calibration among laboratories (6). The alternate IDMS-traceable MDRD Study equation is proposed for laboratories using creatinine methods with calibration traceable to creatinine measured with isotope dilution mass spectroscopy (IDMS). This equation was not developed de novo, but was apparently created by doing a correlation study of specimens tested by both the original MDRD Study creatinine method and an IDMS creatinine method, then inserting the resulting correlation equation into the original MDRD Study equation and simplifying (7). Although this alternative method addresses calibration differences, it will still carry hidden bias as a result of development in a population containing only CKD patients, and also because of varying interindividual nonspecificity in the original MDRD equation.
Study creatinine method. And harmonization still lies somewhere in the future.

If a screening test is to be applied to a population, there should be evidence that it works in that population. If an MDRD eGFR is to be reported with every creatinine result, then the MDRD Study equation should be able to predict GFR with reasonable diagnostic accuracy in any population that is subject to creatinine measurements. However, the LWG states that the MDRD study equation is “. . . not recommended for hospitalized patients” (6). In most hospital-based laboratories, the majority of creatinine results are obtained from hospitalized patients. The MDRD Study equation has poor accuracy in predicting GFR in hospitalized patients with CKD (8) and has not been tested in hospitalized patients without CKD. Because many hospital inpatients are not at steady state with regard to renal function and serum creatinine concentration, there may not be a prediction equation that will work well in this population.

There are many subpopulations for which creatinine production rates may be sufficiently different so that a “one size fits all” prediction equation would be inappropriate. When applied to African-Americans with CKD, the original equation (developed using European-Americans with CKD) underestimated GFR by an average of 21%, requiring a correction factor be included for African-Americans (2, 3). Correction factors may be needed for other ethnic groups, but this issue remains largely uninvestigated. The MDRD Study equations may also be inappropriate for other subpopulations. The LWG notes that application of MDRD eGFR to “children, the elderly >75 years, pregnant women, patients with serious comorbid conditions, or persons with extremes of body size, muscle mass, or nutritional status. . . may lead to errors in GFR estimation” (6).

PERFORMANCE OF eGFR IN HEALTHY POPULATIONS

Screening tests are generally used to detect early disease in individuals who are apparently healthy. It is appropriate to ask what the accuracy of the MDRD Study equation is in predicting GFR for apparently healthy individuals. Five large studies have addressed this issue by looking at the performance of the MDRD Study equation in apparently healthy prospective kidney donors (Table 1; 9–13). In all 5 studies, the MDRD Study Equation showed a substantial negative bias; that is, the eGFR typically underestimated the actual GFR. Because of the bias, as well as considerable imprecision, the MDRD Study equation was poor in its ability to predict measured GFR, as reflected in very low $R^2$ values. The eGFR results were off by 30% or more in up to 49% of the study participants. An analytical test with such poor performance would not be acceptable in most laboratories.

It is not surprising that the MDRD Study equation performs less well in a healthy population than in the CKD population that was used in its development. A possible explanation is that healthy individuals have higher rates of creatinine production, and thus higher creatinine concentrations at a given GFR, leading to the increased imprecision in the eGFR. The NKDEP suggests that these problems can be acceptably handled by not reporting numeric values for eGFR that exceed 60 mL·min·1.73 m$^{-2}$ (3, 6). However, the consistent negative bias in the eGFR values suggests that there will be many individuals with actual GFR $>60$ mL·min·1.73 m$^{-2}$, but with eGFR $<60$ mL·min·1.73 m$^{-2}$. These eGFR values will be reported and may lead to false-positive, presumptive diagnoses of CKD.

The study by Rule et al. (10) included 580 potential kidney donors, none of whom had an actual GFR $<60$ mL·min·1.73 m$^{-2}$. However, 12% had false-positive eGFRs of $<60$ mL·min·1.73 m$^{-2}$. False-positive rates were not explicitly reported for the other studies but can be estimated from figures in the studies of Poggio (12) and Verhave (13) (Table 1). These false-positive populations were not comprised primarily of persons with true GFRs only marginally above the cutoff. Half of the false positives in the Poggio study (12) and 20%–30% of the false positives in the studies of Rule (10) and Verhave (13) had actual GFRs exceeding 90 mL·min·1.73 m$^{-2}$.

The false-positive rate appears to be highly dependent on the creatinine method. It is highest in the Rule study (10), which used creatinine results biased high relative to MDRD creatinine, and lowest in the Poggio study (12), with creatinine results biased low. When using creatinine results mathematically adjusted to match MDRD creatinine, an intermediate false-positive rate of 5%–6% can be

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**Table 1. Comparison of MDRD Study eGFR with directly measured GFR in apparently healthy individuals.**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Bias, %</th>
<th>Results with &gt;30% error, %</th>
<th>False positive rate, %</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al.  (9)</td>
<td>100</td>
<td>−17.1</td>
<td>35</td>
<td>nr$^a$</td>
<td>0.02</td>
</tr>
<tr>
<td>Rule et al. (10)</td>
<td>580</td>
<td>−29</td>
<td>46</td>
<td>12</td>
<td>0.19</td>
</tr>
<tr>
<td>Froissart et al. (11)</td>
<td>162</td>
<td>−5.1</td>
<td>36</td>
<td>nr$^a$</td>
<td></td>
</tr>
<tr>
<td>Poggio et al. (12)</td>
<td>457</td>
<td>−9.0</td>
<td>14</td>
<td>1.3$^b$</td>
<td>0.13</td>
</tr>
<tr>
<td>Verhave et al. (13)</td>
<td>850</td>
<td>−28.8</td>
<td>49</td>
<td>5–6$^c$</td>
<td>0.34</td>
</tr>
</tbody>
</table>

$^a$ nr, not reported.
$^b$ From Fig. 2A of (12).
$^c$ Estimated from Fig. 1D of (13).
The estimated prevalence of CKD would be predictive value is assumed to be 45%, the actual prevalence is likely to be an overestimate. For example, if the positive estimation of eGFR in non-CKD populations, this number remain the same (or be lower if a birthday has occurred in 3 months and is the same, the eGFR will be re-measured in 3 months and is the same, the eGFR will remain the same (or be lower if a birthday has occurred within the interval). The NKDEP recommends against determining a creatinine clearance as an estimate of GFR (2). Given that the direct measurement of GFR is a relatively demanding procedure that is usually available only in research settings, it is possible that many screening false positives may not be corrected.

The NKDEP recommends measuring the urinary albumin/creatinine ratio in those with eGFR < 60 mL·min·1.73 m⁻² (2). Observing considerable albuminuria can increase confidence that the low eGFR is real. But failure to find albuminuria will not negate the diagnosis of CKD. (Although not the topic of this article, measurements of urine albumin concentrations may show as much between-laboratory variability as do current creatinine measurements.)

What will happen to those people who have an incorrect eGFR of < 60 mL·min·1.73 m⁻² that is confirmed with a second incorrect eGFR? It is likely they will be labeled with a diagnosis of confirmed CKD. Being given the diagnosis of a progressive, incurable disease that may eventually prove fatal may have a major negative impact on an individual’s self-image and quality of life. It could also affect insurability or employability. The NKDEP recommends drug treatment for “...any patient with an estimated GFR < 60 mL·min·1.73 m⁻² (2). Individuals with false-positive diagnoses may undergo the inconvenience, expense, and side effects of life-long therapy that they do not need.

Tests for genetic disease and HIV infection raise similar issues. Because of the substantial implications of such diagnoses, there is a consensus (often backed by legislation) that testing for genetic disease or HIV infection should be done only with the explicit consent of the person to be tested. The NKDEP does not discuss the ethical issues implicit in the recommendation to automatically report eGFR with every creatinine measurement, precluding the patient’s right to decide about such testing.

**Lack of a Confirmatory Test**

For any screening test, there should be a confirmatory test or procedure to identify and correct a false-positive screening diagnosis. What is the confirmatory test for an eGFR < 60 mL·min·1.73 m⁻²? If the serum creatinine is re-measured in 3 months and is the same, the eGFR will remain the same (or be lower if a birthday has occurred within the interval). The NKDEP recommends against determining a creatinine clearance as an estimate of GFR (2). Given that the direct measurement of GFR is a relatively demanding procedure that is usually available

**Absence of Evidence**

Providing an eGFR with every creatinine measurement is an untested medical intervention that is being proposed for national and international implementation, despite the lack of clinical trials or other pilot studies. Such studies could provide evidence of both the benefits and risks that would accompany such an intervention. Currently, that evidence is missing. If we automatically provide an eGFR for anyone who has a creatinine measurement, we are in effect making that person a participant in a medical experiment, one for which there is no informed consent and no right of refusal.

**Recommendations**

The goal of identifying persons with early kidney disease in the hopes of slowing progression is a worthy one. However, its implementation by providing an eGFR with every creatinine measurement is premature, whether eGFR is determined by one of the MDRD Study equations or by some other equation. Several things must be accomplished before such an approach can be recommended. As
noted by the NKDEP LWG (6), laboratory measurements of creatinine must be standardized. A new prediction equation must be derived from the standardized creatinine measurements and directly measured GFRs in a population representative of that to which the calculation will be applied. This equation must then be validated in an independent population that is also representative. The equation should also be tested for diagnostic accuracy in major ethnic groups and other appropriate subpopulations that may be subject to the calculation, with correction factors or alternative equations determined when appropriate. It is possible that no single prediction equation can be developed that will be adequate for general application to everyone.

Guidelines need to be developed and published that will allow identification and correction of eGFR results of <60 mL·min·1.73 m⁻² in individuals with an actual GFR that is substantially greater. Guidelines should also identify management strategies that might produce improved outcomes for persons correctly identified as having GFR <60 mL·min·1.73 m⁻², including those individuals with no apparent underlying problems and those whose only underlying problem is old age. It may also be desirable to develop guidelines for use of the prediction equation in determining drug dosing. All guidelines should be based on good clinical evidence.

Efforts are underway to address the issues described above. Alternative approaches for predicting GFR with cystatin C are also under investigation. At present, none of these initiatives have been completed.

Conclusions

With our current knowledge, providing an eGFR with every reported creatinine result would mean undertaking widespread screening of a general population with low prior probability of CKD, with a test of less than optimal specificity. Until we have more consistent creatinine measurements and a prediction equation with better diagnostic accuracy in healthy populations, use of eGFR should be limited to screening high-risk individuals and to following patients with known CKD. It would be reasonable for laboratories to offer an eGFR calculated by an MDRD Study equation when such a calculation is requested by a physician. The physician can determine whether the patient is an appropriate and willing candidate for eGFR calculation and take responsibility for providing appropriate interpretation and follow-up of the results.