

Current Status and Future Perspectives for CKD Testing

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Chronic kidney disease (CKD) is common in the United States. CKD usually is silent until its late stages; thus, many patients with CKD are not aware of their kidney disease. Often, they are found to have CKD only shortly before the onset of symptomatic kidney failure, when there are few opportunities to prevent adverse outcomes. Earlier detection allows more time for evaluation and treatment, but requires explicit testing strategies for asymptomatic individuals at increased risk. CKD is defined as kidney damage or glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² for 3 months or longer. In the majority of patients, CKD can be detected by using 2 simple tests: a urine test for the detection of proteinuria and a blood test to estimate GFR. Understanding the strengths and limitations of CKD testing is critical for appropriate interpretation of the results. The major strength of CKD testing is its feasibility of implementation in public health activities and clinical practice, enabling the detection of CKD by using objective measures without knowledge of the cause of the kidney disease. The major limitation of testing for urine protein is that both total protein and albumin excretion can be increased transiently for a number of factors. The major limitation of current GFR-estimating equations is the inaccuracy of estimates at 60 mL/min/1.73 m² and greater, which is the threshold for the definition of CKD. Repeated testing for urine protein and interpretation of GFR estimates in the context of kidney damage and the clinical context of patient presentation can help overcome these limitations.

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INDEX WORDS: Glomerular filtration rate (GFR); chronic kidney disease; creatinine; detection.

Chronic kidney disease (CKD) usually is asymptomatic until its late stages. Thus, many patients with CKD are detected only shortly before the onset of symptomatic kidney failure, when there are few opportunities to prevent adverse outcomes.^{1,2} Earlier detection allows more time for evaluation and treatment, but would require explicit testing strategies for asymptomatic individuals at increased risk.

CKD testing currently is applied in the US National Health and Nutrition Examination Survey (NHANES) and the National Kidney Foundation (NKF) Kidney Early Evaluation Program (KEEP).^{3,4} Both activities have shown a large burden of CKD and also that the population is largely unaware of its presence, emphasizing the need for widespread public health activities. Application of CKD testing in local, national, and international screening programs may improve the detection of CKD, which then potentially may be translated into improved public health related to CKD.^{5,6} The Centers for Disease Control and Prevention is currently working with the NKF to implement a KEEP-like model for screening individuals at risk of CKD in a state-level demonstration project to test the impact of CKD testing programs. Understanding the strengths and limitations of CKD testing is critical for appropriate implementation of these programs. The goal of this report is to discuss CKD testing in clinical practice and its application to public

health initiatives, with attention to limitations and appropriate interpretation. We also discuss recent results and future directions with regard to population screening for CKD. We emphasize testing for both the presence of kidney damage and level of kidney function in adults at increased risk of CKD.

CKD DEFINITION AND TESTING

CKD is defined as the presence of kidney damage or glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² for 3 or more months, irrespective of cause.^{2,7} Markers of kidney damage include abnormalities in serum or urine or on imaging studies and reflect the underlying pathological state. Proteinuria is the earliest marker of kidney damage in patients with diabetes, hypertension, and glomerular diseases; thus, it is the most common marker of kidney damage in adults.² GFR is difficult to measure, but can be estimated easily from serum creatinine level, age, sex, race, and body size.

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Currently, CKD is classified by its severity, indicated by the level of GFR. However, CKD is a heterogeneous condition with varying expression in individual patients related in part to the cause and pathological characteristics of kidney disease, rate of progression, and presence of comorbid conditions. Despite its heterogeneous expression, the definition irrespective of cause allows for the detection of most cases of CKD with the use of 2 simple tests: a urine test for the detection of proteinuria and a blood test to estimate GFR. These 2 simple tests are feasible for implementation in public health activities and clinical practice, enabling the detection of CKD by using objective measures without knowledge of its cause. Importantly, these 2 tests facilitate the detection of CKD by all health care practitioners, not just nephrologists, without first requiring determination of its cause. In this article, we focus on the recommendations for routine testing in the general population at increased risk of CKD.

TESTING FOR KIDNEY DAMAGE

Proteinuria

Proteinuria refers to increased excretion of any urinary protein, including albumin and other serum proteins, as well as proteins synthesized by the tubule (Tamm-Horsfall protein) or in the lower urinary tract. Here, we refer to testing for proteinuria as tests for the detection of all types of proteinuria, including albumin. We refer to testing for albuminuria as tests for the detection of albumin only.

A persistent increase in protein excretion usually is a marker of kidney damage, with the specific proteins dependent on the type of kidney disease. Increased albumin excretion is a sensitive and specific marker for kidney disease caused by diabetes, other glomerular diseases, and hypertension. Increased excretion of nonalbumin proteins in the absence of albumin excretion occurs in patients with some tubulointerstitial diseases associated with defective reabsorption of filtered low-molecular-weight proteins. In addition to indicating kidney damage and providing clues to the cause of the kidney disease, proteinuria provides important information for the evaluation and management of CKD. Full discussion is beyond the scope of this report.⁸

There are several methods for measurement of urine protein, leading to variations in the definition of the normal range.² The most commonly used tests measure total protein (including albumin) or albumin alone. Tests for albuminuria have greater sensitivity and specificity for kidney disease caused by diabetes, hypertension, and glomerular diseases than tests for total protein, but are more expensive. Assays for total protein and albumin vary across laboratories, which makes it difficult to compare results and determine the normal range. Assays for albumin can be standardized; however, there is no gold standard for total urine protein because the composition of urine protein varies among individuals.

There are also multiple methods for the collection of urine. The 24-hour collection is regarded as the gold standard, but it is difficult to implement in routine practice. Measurement of albumin or total protein in a spot sample avoids the need for collection of a timed urine specimen, but is affected by the state of hydration. Factoring the concentration of albumin or total protein by urine creatinine concentration (the ratio of albumin to creatinine or total protein to creatinine) eliminates this source of variation. [Table 1](#) lists thresholds for the definition of albuminuria and proteinuria according to collection method.² Measurement of the ratio of albumin to creatinine or total protein to creatinine in a spot urine sample is the recommended method of testing for CKD.²

Albumin-creatinine ratio and protein-creatinine ratio are affected by the level of creatinine excretion in addition to the level of protein or albumin excretion. Creatinine excretion reflects creatinine generation by muscle mass and, to a lesser extent, dietary intake. Muscle mass differs by age, sex, and race. Sex-specific thresholds for the definition of abnormal albumin-creatinine ratios have been suggested to account for differences in creatinine excretion.^{9,10} Suggested sex-specific thresholds are 17 mg/g or greater for men and 25 mg/g or greater for women, rather than the usual cutoff value of 30 mg/g regardless of sex. A population-based study in Karachi, Pakistan, compared albumin-creatinine ratio with 24-hour urine collection. Using an albumin excretion rate greater than 30 mg/d as the gold standard, an albumin-creatinine ratio greater than 30 mg/g had sensitivity and specificity of 60% and

Table 1. Definitions of Proteinuria and Albuminuria

Urine Collection Method		Normal	Microalbuminuria	Macroalbuminuria or Clinical Proteinuria
Total protein	24-h Excretion (varies with method)	<300 mg/d	NA	>300 mg/d
	Spot urine dipstick	<30 mg/dL	NA	>30 mg/dL
	Spot urine protein-creatinine ratio (varies with method)	<200 mg/g	NA	>200 mg/g
Albumin	24-h Excretion	<30 mg/d	30-300 mg/d	>300 mg/d
	Spot urine albumin-specific dipstick	<3 mg/dL	>3 mg/dL	NA
	Spot urine albumin-creatinine ratio (varies by sex*)	<17 mg/g (men), <25 mg/g (women)	17-250 mg/g (men), 25-355 mg/g (women)	>250 mg/g (men), >355 mg/g (women)

Note: Conversion factor for units: urine protein and albumin in mg/dL to g/L, ×100.

*Sex-specific cutoff values are from a single study. Use of the same cutoff value for men and women leads to greater prevalence values for women than men. Current recommendations from the American Diabetes Association define cutoff values for spot urine albumin-creatinine ratio for microalbuminuria and albuminuria as 30 and 300 mg/g without regard to sex, respectively.

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97% in men and 46% and 95% in women, respectively.¹¹ Sensitivity and specificity for a cutoff value of 17 mg/g in men were 66% and 93%, and for a cutoff value of 25 mg/g in women, 52% and 95%, respectively. There are also likely to be important differences according to age and race. For example, in the same population in Pakistan, Indo-Asians had lower creatinine excretion than whites.¹² Nevertheless, despite these differences, sensitivity and specificity are similar to those published for white populations.¹³ More work is required to better understand the implications of normal variations in albumin and creatinine excretion for normal values in diverse populations.

Both total protein and albumin excretion can increase transiently because of a number of factors, including urinary tract infection; such hemodynamic stress as exercise, fever, and congestive heart failure; and such transient metabolic perturbations as ketosis and hyperglycemia. In a subset of NHANES III, a total of 1,241 participants underwent repeated testing for albuminuria within 2 months. In individuals with microalbuminuria at the initial visit, 63% had evidence of microalbuminuria or macroalbuminuria at the second visit. All patients with macroalbuminuria had evidence of microalbuminuria or macroalbuminuria at the second visit. Because of variation, proteinuria is defined as persistent if 2 or 3 tests have abnormal results during a 3- to 6-month period.¹⁴ Proteinuria must be persistent over a minimum of 3 months to indicate kidney damage in patients with CKD.⁷ Figure 1 shows the algorithm

recommended from the American Diabetes Association for sequential use of tests to detect kidney disease in adults and children with diabetes.¹⁵

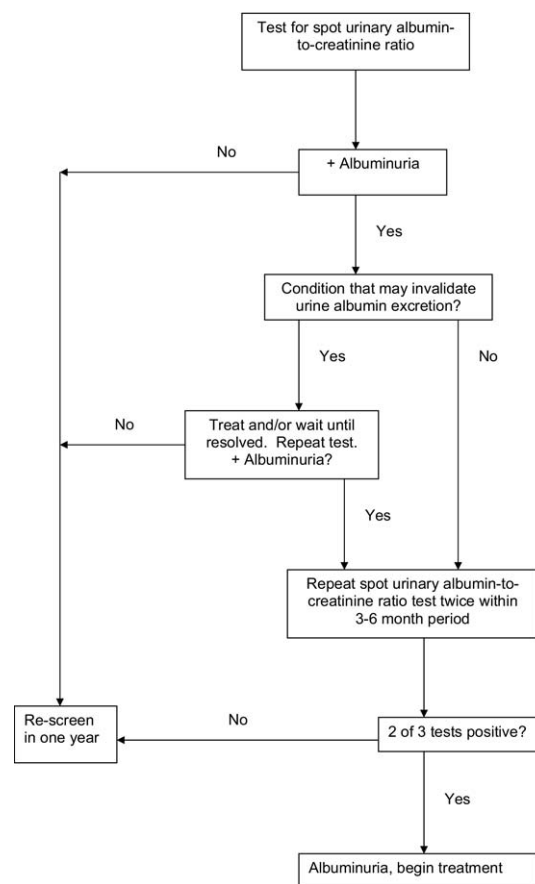


Figure 1. Algorithm for the evaluation for proteinuria. Copyright © 2004 American Diabetes Association; modified and reproduced with permission.¹⁵

We recommend that this algorithm be used for all people with risk factors for kidney disease.

Other Markers of Kidney Damage

Clinical judgment should determine the utility of testing for other markers of kidney damage for the detection of CKD, such as imaging studies, other urine or serum markers, or kidney biopsy.² For example, people with a family history of polycystic kidney disease should undergo ultrasound examination to detect the presence of cysts, whereas people with a family history of Alport syndrome should undergo urinalysis to detect hematuria. Consultation with a nephrologist is recommended if there are questions about the most appropriate tests for the detection of specific diseases other than those mentioned here.

TESTING THE LEVEL OF KIDNEY FUNCTION

GFR is considered the best overall measure of kidney function. GFR cannot be measured directly, but is ascertained as the clearance of exogenous filtration markers. Such measurements are cumbersome and expensive and not usually performed in routine clinical practice. Serum levels of endogenous filtration markers, such as creatinine, traditionally have been used to estimate GFR. Cystatin C is a more recently discovered filtration marker now undergoing extensive evaluation for GFR estimation. GFR estimates from serum levels of endogenous filtration markers are affected by physiological processes other than GFR, including the generation, tubular reabsorption and secretion, and extrarenal elimination of the marker, as well as by means of assay of the filtration marker (Box 1).²⁰

GFR Estimation From Serum Creatinine

Creatinine is an 113-Da compound generated in muscle from the breakdown of the amino-acid derivative creatine and distributed throughout total-body water. Limitations of serum creatinine as a filtration marker include variation in generation, which is largely dependent on muscle mass and meat intake, as described; proximal tubular secretion; and extrarenal elimination in the gastrointestinal tract,²⁰ as well as variation among laboratories in assays.²¹ Estimating equations incorporate creatinine in association with age, sex, race, and body size as surrogates for creatinine generation.

Box 1. GFR Estimating Equations

1. The original MDRD Study equation^{16,17}:

$$\text{eGFR} = 186 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \\ \times 1.212 \text{ (if African American)} \\ \times 0.742 \text{ (if female)}$$
2. The "reexpressed" MDRD Study equation for standardized SCr¹⁸:

$$\text{eGFR} = 175 \times \text{standard SCr}^{-1.154} \times \text{age}^{-0.203} \\ \times 1.212 \text{ (if African American)} \\ \times 0.742 \text{ (if female)}$$
3. CKD-EPI cystatin equation not adjusted for age, sex, and race¹⁹:

$$\text{eGFR} = 76.7 \times \text{CysC}^{-1.19}$$
4. CKD-EPI cystatin equation adjusted for age, sex, and race¹⁹:

$$\text{eGFR} = 127.7 \times \text{CysC}^{-1.17} \times \text{age}^{-0.13} \\ \times 0.91 \text{ (if female)} \\ \times 1.06 \text{ (if African American)}$$
5. CKD-EPI cystatin and creatinine equation adjusted for age, sex, and race¹⁹:

$$\text{eGFR} = 177.6 \times \text{SCr}^{-0.65} \times \text{CysC}^{-0.57} \times \text{age}^{-0.20} \\ \times 0.80 \text{ (if female)} \\ \times 1.11 \text{ (if African American)}$$

Note: GFR is expressed as mL/min/1.73 m²; Age is expressed in years; weight is expressed in kilograms. Conversion factors for units: GFR in mL/min/1.73 m² to mL/s/1.73 m², $\times 0.01667$; SCr in mg/dL to $\mu\text{mol/L}$, $\times 88.4$; serum CysC in mg/L to nmol/L, $\times 74.9$.

Abbreviations: CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CysC, serum cystatin C; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine.

One commonly used equation used to estimate GFR, the Modification of Diet in Renal Disease (MDRD) Study equation, was developed in patients with CKD and has been reexpressed for use with a standardized serum creatinine assay (Box 1).^{16-18,22} The MDRD Study equation has now been evaluated in numerous populations, including African Americans, Europeans, Asians, patients with and without diabetes or kidney disease, kidney transplant recipients, and potential kidney donors. Overall, studies of American or European-based populations show that the MDRD Study equation has reasonable accuracy in nonhospitalized patients known to have CKD regardless of diagnosis,²³ but less accuracy in populations without kidney disease, such as

Table 2. Performance of the MDRD Study Equation Using Calibrated and Noncalibrated Creatinine Values

Study	Measured GFR (mL/min/1.73 m ²)	No. of Patients	Median Difference (CI)	
			Calibrated	Noncalibrated
Pooled	68 (40)	5,504	2.7 (2.4 to 3.1)	4.4 (4 to 4.7)
MDRD Study ²⁷	40 (21)	1,085	0.0 (−0.4 to 0.4)	0.0 (−0.4 to 0.4)
AASK ²⁸	57 (24)	1,205	1.1 (0.4 to 1.7)	3.9 (3.2 to 4.5)
DCCT ²⁹	124 (20)	787	12.4 (10.2 to 13.9)	17.9 (16.3 to 20.3)
DRDS ³⁰	115 (28)	126	−0.7 (−5.7 to 5)	13.6 (10 to 20.9)
CSG ³¹	78 (33)	266	9.8 (7.3 to 12.3)	9.7 (7.7 to 12.7)
CRIC ³²	50 (21)	446	3.7 (2.6 to 5.2)	3.3 (2.4 to 4.7)
CC CKD ²⁵	34 (27)	695	0.2 (−0.5 to 0.9)	0.6 (−0.3 to 1.2)
CC Donors ²⁵	106 (18)	303	14.8 (12.7 to 16.9)	8.6 (6.7 to 11.4)
Mayo CKD ²⁶	48 (26)	221	0.1 (−1.0 to 1.2)	2.9 (1.3 to 4.7)
Mayo Donors ²⁶	102 (17)	372	13.2 (12 to 15.4)	28.9 (26.9 to 30.8)

Note: Conversion factor for unit: GFR in mL/min/1.73 m² to mL/s/1.73 m², ×0.01667.

Abbreviations: AASK, African American Study of Kidney Diseases and Hypertension; CRIC, Chronic Renal Insufficiency Cohort Study; CC, Cleveland Clinic; CSG, Collaborative Study Group: Captopril in Diabetic Nephropathy Study; DCCT, Diabetes Control and Complications Trial; DRDS, Diabetic Renal Disease Study; Mayo, Mayo Clinic; MDRD, Modification of Diet in Renal Disease.

Adapted with permission from Stevens et al.³³

young patients with type 1 diabetes without albuminuria or people undergoing evaluation for kidney donation.²⁴⁻²⁶

Calibration of serum creatinine concentration is a key factor affecting the accuracy of GFR estimates using all GFR-estimating equations. In part, some of the differences described in results of studies may have been caused by differences in calibration of the creatinine assay. A pooled data set of 10 studies with 5,504 people with or without CKD from the CKD Epidemiology Collaboration (CKD-EPI) showed improved performance of the MDRD Study equation after calibration to standardized creatinine. The greatest impact was observed in studies with greater mean measured GFR, with some studies showing improved performance (Table 2).³³ Other reports have shown substantial effects of calibration on population estimates.³⁴⁻³⁶

After calibration, the MDRD Study equation provided unbiased and reasonably accurate estimates in the CKD-EPI pooled data set when estimated GFR (eGFR) was less than 60 mL/min/1.73 m² (Table 3; Fig 2).³⁷ For eGFR less than 60 mL/min/1.73 m², performance was consistent across a wide range of subgroups defined by age, sex, race, body mass index, presence or absence of diabetes, or history of kidney transplantation. Precision was lower and bias was higher at greater eGFRs for all subgroups (Table 4).³⁷

There are several possible explanations for decreased accuracy at higher GFR estimates, including: (1) interlaboratory variation in the calibration of serum creatinine assay, which has a larger effect at greater GFRs, as described³³; (2) greater biological variation and errors in measurement of GFR at a greater range of GFRs; and (3) limitations of applying an equation developed in people with CKD to a population predominantly without CKD.²⁰ These consider-

Table 3. Performance of the MDRD Study Equation in the CKD-EPI Pooled Data Set, Overall and Stratified by eGFR Greater and Less Than 60 mL/min/1.73 m²

GFR Range (mL/min/1.73 m ²)	No. of Patients	Difference		
		Median	Interquartile Range	P ₃₀
All	5,504	2.7	16.4	83
≥60	2,630	8.3	26.6	84
<60	2,874	0.9	9.6	82

Note: Data set consists of data from 5,504 people from 10 studies.^{33,37} Difference is calculated as measured GFR minus estimated GFR. Median values measure bias and interquartile ranges measure precision. P₃₀ is calculated as the percentage of estimated GFR within 30% of measured GFR. Conversion factor: GFR in mL/min/1.73 m² to mL/s/1.73 m², ×0.01667.

Abbreviations: MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

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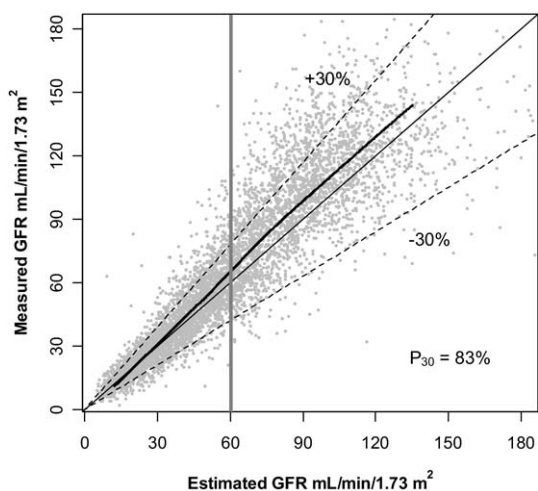


Figure 2. Modification of Diet in Renal Disease Study 4-variable equation measured glomerular filtration rate (GFR) versus estimated GFR in 5,504 individuals. Thin black diagonal line, line of identity; grey dots, individual data points; thick black line, regression line through the points plotted using 97.5% of the data; thick gray vertical line, at 60 mL/min/1.73 m², which is the cutoff for the definition of kidney disease. Conversion factor: GFR in mL/min/1.73 m² to mL/s/1.73 m², $\times 0.01667$.

ations are relevant for all GFR-estimating equations.

The MDRD Study equation is not likely to perform as well in other populations because of differences in diet or muscle mass. For example, as mentioned, data from the population-based study in Pakistan showed lower levels of creatinine excretion than described in white populations.¹² The MDRD Study equation has not been explicitly validated in that population; however, given these data, it would be hypothesized that the equation would overestimate measured GFR. Two recent studies evaluating the MDRD Study equation in China and Japan showed conflicting results, with 1 study showing underestimation of measured GFR and the second showing overestimation.^{38,39} Possible explanations for these conflicting results are differences in creatinine assay, GFR measurement procedures, or among populations in creatinine generation. Studies of creatinine excretion in these populations have not been performed, but would facilitate distinguishing among these possibilities.

GFR Estimation From Cystatin C

Cystatin C is a 13-kDa protease inhibitor produced in all cells. It is filtered by glomeruli

and extensively catabolized by renal tubules with little urinary excretion. Effects of physiological processes other than GFR on cystatin C level are not well known. Serum cystatin C levels are not believed to be related to muscle mass or diet; however, studies have shown that greater serum levels are associated with greater C-reactive protein and body mass index, hyperthyroidism, and steroid use.^{40,41} Other studies now report substantial differences in available assays.⁴² Serum cystatin C levels estimate GFR better than serum creatinine level alone in most studies; however, there is little or no improvement over creatinine-based estimating equations.⁴³ In a pooled data set of 4 studies with 3,134 people with CKD from CKD-EPI, cystatin C level alone provided GFR estimates that were nearly as accurate as serum creatinine level adjusted for age, sex, and race.¹⁹ A small bias was present in age, sex, and race subgroups when using cystatin C level alone, which decreased with the addition of these terms in the estimating equation. Examination of this and other published cystatin C–based GFR-estimating equations shows marked variation in GFR estimates calculated for any specific serum cystatin C value.⁴³ Together, these data suggest that the generation, renal handling, or assay of cystatin C may differ among populations. Despite these uncertainties, many studies have shown that cystatin C level is a better predictor of adverse events than serum creatinine level or GFR estimated from serum creatinine level, particularly in elderly or cardiac populations.^{43–48} Whether the strong association of serum cystatin C levels with adverse events reflects its relationship with the level of GFR or factors other than GFR has not yet been determined.⁴⁹ Overall, more work is required to understand how to best use cystatin C level as a filtration marker in clinical practice.

INTERPRETATION OF CKD TESTS AND INTEGRATION INTO THE CLINICAL ACTION PLAN

Table 5 shows a simple guide to the interpretation of CKD test results. In patients with albuminuria or other markers of kidney damage persistent for 3 months or more, CKD should be diagnosed irrespective of eGFR. Patients without markers of kidney damage and with eGFR of 60

Table 4. Performance of the MDRD Study Equation in Subgroups

	Estimated GFR < 60 mL/min/1.73 m ² *		Estimated GFR ≥ 60 mL/min/1.73 m ² †	
	No. of Patients	Median Difference (95% CI)	No. of Patients	Median Difference (95% CI)
Overall	2,874	0.9 (0.6 to 1.1)	2,630	8.3 (7.4 to 9.2)
Age (y)				
<40	585	0.7 (0.1 to 1.5)	1,473	10.6 (9.2 to 12.2)
40-65	1,709	1.3 (1.0, 1.8)	1,042	6.4 (5.2 to 7.8)
>65	580	-0.4 (-0.8 to 0.4)	115	-0.3 (-5.3 to 2.3)
Women				
Yes	1,212	1.0 (0.7 to 1.7)	1,179	11.3 (9.9 to 12.6)
No	1,662	0.7 (0.4 to 1.1)	1,451	6.2 (5.2 to 7.5)
Race				
White and other	1,668	0.6 (0.3 to 0.9)	1,799	12.1 (10.9 to 12.9)
African American	1,085	1.2 (0.7 to 1.9)	643	0.1 (-1.4 to 1.5)
Asian American	44	4.2 (1.2 to 7.3)	18	8.5 (-3.2 to 15..2)
Native American, Pacific Islander, or Hispanic	77	1.5 (-1 to 2.5)	170	1.0 (-2.8 to 5.3)
Diabetes				
Yes	510	1.7 (0.8 to 2.4)	1,071	10.8 (8.7 to 12.5)
No	2,364	0.7 (0.4 to 1.1)	1,559	6.8 (5.7 to 8.1)
Transplant				
Yes	169	0.4 (-1.3 to 2.1)	72	-7.6 (-11.7 to -2.9)
No	2,705	0.9 (0.6 to 1.2)	2,558	8.7 (7.9 to 9.6)
Body mass index (kg/m ²)				
<20	96	-1.4 (-2.4 to 2)	90	4.8 (-0.9 to 7.3)
20-25	740	-0.2 (-0.6 to 0.4)	927	9.6 (8.2 to 11)
26-30	999	1.3 (0.8 to 1.9)	938	9.0 (7.6 to 10.8)
>30	1,039	1.3 (0.9 to 2)	675	6.6 (4.2 to 8.1)

Note: Difference calculated as measured GFR minus estimated GFR. Conversion factor: GFR in mL/min/1.73 m² to mL/s/1.73 m², ×0.01667.

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

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*Measured GFR in this subgroup is 37 ± 18 mL/min/1.73 m².

†Measured GFR in this subgroup is 101 ± 28 mL/min/1.73 m².

mL/min/1.73 m² or greater are unlikely to have CKD. There is some uncertainty for patients without markers of kidney damage and with

Table 5. Interpretation of CKD Testing

Marker of Kidney Damage	GFR (mL/min/1.73 m ²)	CKD	What to Do?
+	<60	Yes	Clinical action plan*
+	≥60	Yes	Clinical action plan
-	<60†	Yes	Clinical action plan
-	≥60	No	

Note: Conversion factor: GFR in mL/min/1.73 m² to mL/s/1.73 m², ×0.01667.

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

*For clinical action plan, see Table 2 of Levey et al.⁵⁰

†Because of bias in the MDRD Study equation in non-CKD populations, some individuals with normal measured GFR may have GFR estimates just less than 60 mL/min/1.73 m². Individual decision making is required in such cases.

eGFR less than 60 mL/min/1.73 m². The lower accuracy of current estimating equations at greater GFRs may make it difficult to interpret GFR estimates just less than 60 mL/min/1.73 m². For such estimates, interpretation of GFR estimates should be made by using the clinical context. Some patients will have measured GFR less than 60 mL/min/1.73 m² and therefore would have CKD (true-positive test result). Others may have measured GFR greater than 60 mL/min/1.73 m² and therefore would not have CKD (false-positive test result). Further interpretation and decision making will depend on the patient's risk of CKD. An eGFR just less than 60 mL/min/1.73 m² is more likely to be a true-positive result in a patient at increased risk of CKD (ie, a patient with hypertension, diabetes, cardiovascular disease, or a family history of CKD) than in a patient not at increased risk.

Current guidelines recommended routine testing in patients at increased risk of CKD. Restricting routine testing to patients at increased risk of CKD is likely to decrease false-positive results and enable more efficient use of resources.^{2,7,20,52} In patients at increased risk of CKD and with an eGFR less than 60 mL/min/1.73 m², it is appropriate for clinicians to proceed with the CKD clinical action plan (Table 5). In patients not at increased risk of CKD and with an eGFR just less than 60 mL/min/1.73 m², clinicians should make further evaluation and management decisions that are appropriate for the individual patient and, for example, could decide to defer further evaluation for CKD. Nonetheless, it may be prudent to monitor eGFR more frequently, adjust the dosage of medications excreted by the kidney, and avoid medications toxic to the kidney. Newer equations likely will improve the estimation of GFR in this range and decrease the likelihood of false-positive diagnoses.⁵¹

LIMITATIONS

There are 4 main limitations to the current testing recommendations. First, there is a variable rate of false-positive test results for both urine protein and eGFR, depending on the population screened. Repeated measurements, with confirmation of persistence of abnormal results over 3 months, will diminish the false-positive rate of urine protein testing. Repeated measurement of serum creatinine may not decrease the false-positive rate because the differences in creatinine generation that are at the root of the error in the estimate are not likely to change during a short time frame. As described, attention to the clinical setting can facilitate proper interpretation of eGFR.

Second, there is uncertainty about the implications of CKD for patient outcomes associated with CKD. Although studies have documented increased risk of all-cause mortality, clinical cardiovascular disease events, complications of low GFR, and progression to kidney failure with decreased GFR and with proteinuria, it is difficult to quantify a prediction for an individual person. At present, there is no equivalent to a Framingham risk equation for clinical cardiovascular disease events to relate the risk of any or all CKD outcomes to the combination of level of GFR and proteinuria. In addition, the cost-

effectiveness of these testing strategies has been not explicitly tested.

Finally, the thresholds for abnormal and normal levels of GFR and urine protein were derived primarily from studies of adults in the United States and Europe and may not be applicable to all ages or different geographic, racial, or ethnic groups.

CURRENT ACTIVITIES AND FUTURE DIRECTIONS

The limitations related to the measurement and interpretation of CKD test results are actively being addressed. The laboratory work group of the National Kidney Disease Education Program (NKDEP) of the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) has developed a process to standardize the serum creatinine assay to a high-quality reference standard of the National Institute of Standards and Technology (NIST), with the goal of implementing assay standardization in all clinical laboratories.⁵³ This work is critical to optimizing the accuracy of GFR-estimating equations based on serum creatinine level and is expected to be completed by 2009. The work group is now addressing the challenges of standardization of albumin and creatinine measurements in urine. This will be a major step forward in the interpretation of urine test results and will facilitate the development of uniform reporting formats and normal values for age, sex, and race.⁵⁴ The International Federation of Clinical Chemistry currently is engaged in a similar process for the standardization of cystatin C.

The CKD-EPI collaboration is a research team supported by the NIDDK to develop improved GFR-estimating equations from creatinine level, cystatin level, or both. One of the key goals is to improve the accuracy of GFR estimates near 60 mL/min/1.73 m² to improve the identification of patients with CKD. Other investigations also should focus on how to combine GFR estimates from these markers to create the most accurate result across the range of GFRs. Investigations also should focus on the discovery and development of new filtration markers, which can be used in combination with creatinine or cystatin level to further improve the accuracy and precision of GFR estimates.

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