[A technical review]

Estimated Glomerular Filtration Rate (eGFR)
in the Detection and Assessment of Chronic Kidney Disease in Adults

Introduction

Chronic kidney disease (CKD) is prevalent in the US population and is rising—especially given the aging of that population. It is a disease whose progression to the end-stage renal disease (ESRD) if detected early, can be slowed or halted[1] by such interventions as blood pressure control, appropriate use of ACE inhibitors, angiotensin II receptor blockers (ARBs),[1] glycemic control (in diabetics), treatment of lipid abnormalities and concomitant cardiovascular disease. Early referral to a nephrologist may also lead to an improved outcome, especially in those patients who are in the advanced stages of the disease.

One difficulty that has traditionally faced physicians has been the inability to identify patients in the early stages of CKD. Serum creatinine has proved to be a relatively insensitive marker, especially in the elderly.[2]

In 2002, the National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) published clinical practice guidelines on chronic kidney disease.[3] These guidelines recommend estimating the level of glomerular filtration rate (GFR) by employing prediction equations that incorporate serum creatinine measurements.[3-6]

This method of determining GFR was judged preferable to using serum creatinine alone or measuring creatinine clearance. The guidelines also emphasize the estimation of GFR for

- Early detection of CKD
- Classification of CKD severity
- Estimation of disease progression
- Management of disease complication
- Initiation of referral to nephrologists

To assist in earlier recognition of CKD, it is strongly recommended that clinical laboratories automatically report an estimated glomerular filtration rate (eGFR), along with values for serum creatinine, when serum creatinine is measured.[7] The eGFR should be based on the abbreviated Modification of Diet in Renal Disease (MDRD) study equation[5,6] that adjusts for body surface area without requiring measurement of height, weight or 24-hour urine collection. The GFR number reported should be multiplied by 1.212 if the patient is African American.[3] By noting the estimated GFR, the clinician can more easily identify and stage CKD based on published guidelines (Table 1). Although the estimated GFR allows health care providers to assess kidney function with **greater ease and accuracy** than just a serum creatinine or a historical 24-hour urine creatinine clearance, the estimated GFR is still not ideal. See the limitations section below.

Table 1. Association of Glomerular Filtration Rate (GFR) and Staging of Kidney Disease*

GFR (mL/min/1.73 m²)	With Kidney Damage	Without Kidney Damage
≥ 90	Stage One	Normal
60-89	Stage Two	"Decreased GFR"
30-59	Stage Three	Stage Three
15-29	Stage Four	Stage Four
<15 (or dialysis)	Stage Five	Stage Five

*Each stage assumes the associated GFR level has been in effect for at least three months. Shaded areas above indicate kidney disease.[3]

Table 2. Criteria for Chronic Kidney Disease*

1. Kidney damage for at lease three months, as defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR), manifested by either
   - Pathological abnormalities or
   - Markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests
2. GFR <60 mL/min/1.73 m² for at least three months, with or without kidney damage[3]

*National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. *Am J Kidney Dis.* 2002; 39 (Suppl 1):S1-S266. Reprinted with permission.

Table 3. Classification, Prevalence, and Action Plan for Staging of Chronic Kidney Disease in Adults*

Stage	Description	GFR (mL/in/1.73 m²)	Prevalence		Action**
			N	%	
—	At increased risk for developing CKD	≥ 90 (with CKD risk factors)	—		Screening CKD risk reduction
1	Kidney damage with normal or elevated GFR	≥90	5900	3.3	Diagnosis/treatment; Treatment of comorbid conditions; Slowing progression; CVD risk reduction
2	Kidney damage with mildly reduced GFR	60-89	5300	3.0	Estimating progression
3	Moderately reduced GFR	30-59	7600	4.3	Evaluating and treating complications
4	Severely reduced GFR	15-29	400	0.2	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	300	0.1	Replacement (if uremia present)

*National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. *Am J Kidney Dis.* 2002; 39 (Suppl 1):S1-S266. Reprinted with permission.
**Includes actions from preceding stages.

Table 4. Potential Risk Factors for Susceptibility to and Initiation of Chronic Kidney Disease*	
Clinical Factors	**Sociodemographic Factors**
Diabetes Hypertension Autoimmune diseases Systemic infections Urinary tract infections Urinary stones Lower urinary tract obstruction Neoplasia Family history of chronic kidney diseases Recovery from acute kidney failure Reduction in kidney mass Exposure to certain drugs Low birth weight	Older Age US ethnic minority status: African American, American Indian, Hispanic, Asian, or Pacific Islander Low income/education Exposure to certain chemical and environmental conditions
*National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. *Am J Kidney Dis.* 2002; 39 (Suppl 1):S1-S266. Reprinted with permission.[3]	

Clinicians are referred to published guidelines by Kidney Disease Outcomes Quality Initiative or K/DOQI sponsored by the National Kidney Foundation, National Kidney Disease Education Program (NKDEP) and is also invited to use the Web-based clinical action plan generator based on estimated GFR (www.kidney.org/professionals/doqi/action_plan_web.html).[8]

In February 2007, NKDEP published the revised Suggestions for Laboratories as a guideline for all parties interested in accurately reporting eGFR. This document is updated with the most recent recommendations on creatinine methods calibration to be traceable to an isotope dilution mass spectrometry (IDMS) reference method.[7] The NKDEP in collaboration with the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the European Communities Confederation of Clinical Chemistry (EC4), has launched the Creatinine Standardization Program to reduce interlaboratory variation in creatinine assay calibration and provide more accurate estimates of eGFR.[9]

Discussion

Chronic Kidney Disease as a Public Health Problem. It has been estimated that more than 19 million individuals (approximately 11% of adults in the US) suffer from the early stages of CKD.[2,10] Outcomes of CKD include not only kidney failure, but can also include complications of decreased kidney function and cardiovascular disease (CVD).[11] The incidence and prevalence of kidney failure is rising in the US, with poor outcomes and high cost. The number of individuals with kidney failure treated by dialysis and transplantation is projected to increase from 340,000 in 1999 to 651,000 in 2010.[12] Despite these alarming statistics, there is increasing evidence indicating that some of the adverse outcomes of CKD can be prevented or delayed through early detection and treatment.

Definition and Staging of CKD

CKD is defined as the presence of kidney damage or decreased level of kidney function for three months or more, irrespective of diagnosis (Table 2). Among patients with CKD, the stage of disease is defined according to the level of GFR. Table 3 shows the classification of stages of CKD, the prevalence of each stage, and actions to improve outcomes appropriate to each stage of disease. Stages one through five identify severity of CKD; unstaged category designates individuals who are at increased risk for developing CKD (Table 4). The NKF-K/DOQI guidelines emphasize developing a clinical action plan for each patient, based on the stage of disease as defined by this classification.

Interpretation of GFR Estimates in Adults

Normal GFR in young adults is approximately 120 to 130 mL/min/1.73 m^2 and declines with age (Figure 1).[2,3] In addition, GFR may be reduced due to conditions other than CKD (Table 5). A GFR of <60 mL/min/1.73 m^2 for three or more months is defined as CKD, irrespective of age and cause, because of its association with increased risk of adverse outcomes.[3]

Original MDRD Study Equation (Without Traceability to IDMS)

Note: This equation should be used with creatinine methods that **have not been calibrated** to be traceable to IDMS. It is appropriate to use this equation because most methods in this category will produce creatinine results that have bias similar to that of the method used in developing the original MDRD Study equation. If you have any questions about the traceability of the calibration for the creatinine method in use by your laboratory, NKDEP recommends that you contact the reagent and/or calibrator manufacturer for assistance.

When S_{cr} is in mg/dL (conventional units)[3]:

$$eGFR\ (mL/min/1.73\ m^2) = 186 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742\ \text{if female}) \times (1.210\ \text{if African American})$$

Calculator-friendly Formula:

$$eGFR\ (mL/min/1.73\ m^2) = \exp(\ln(186) - ((1.154 \times \ln(S_{cr})) - ((0.203 \times \ln(Age)) \times (\ln(0.742\ \text{if female})) \times (1.210\ \text{if African American})$$

When S_{cr} is in µmol/L (SI units):

$$eGFR\ (mL/min/1.73\ m^2) = 186 \times (S_{cr}/88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742\ \text{if female}) \times (1.210\ \text{if African American})$$

IDMS-Traceable MDRD Study Equation

Note: This equation should be used only with those creatinine methods that **have been calibrated** to be traceable to IDMS. During the transition to IDMS-traceable calibration, methods that produce results that have acceptable bias when compared to an IDMS-traceable method should use the IDMS-traceable MDRD Study equation. If you have any question about the traceability of the calibration for the creatinine method in use by your laboratory, NKDEP recommends that you contact the reagent and/or calibrator manufacturer for assistance.

When S_{cr} is in mg/dL (conventional units)[3]:

$$eGFR\ (mL/min/1.73\ m^2) = 175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742\ \text{if female}) \times (1.210\ \text{if African American})$$

Calculator-friendly Formula:

$$eGFR\ (mL/min/1.73\ m^2) = \exp(\ln(175) - ((1.154 \times \ln(S_{cr})) - ((0.203 \times \ln(Age)) \times (\ln(0.742\ \text{if female})) \times (1.210\ \text{if African American})$$

When S_{cr} is in µmol/L (SI units):

$$eGFR\ (mL/min/1.73\ m^2) = 175 \times (S_{cr}/88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742\ \text{if female}) \times (1.210\ \text{if African American})$$

The equations require four variables[7]: serum or plasma creatinine (S_{cr}), age in years (18 to 70 years old), gender, and race (African American or not).

Estimating GFR from Prediction Equations

GFR estimates are included on the report form using the MDRD study equation and calibrated serum creatinine. Use of the MDRD study equation pro-

Table 5. Conditions Other than Kidney Disease that Affect GFR*
Pregnancy Alterations in kidney perfusion (heart failure, cirrhosis) Marked excess or deficit of extracellular fluid volume Nonsteroidal anti-inflammatory drugs Acute protein load and habitual protein intake Blood glucose control (in diabetics) Level of arterial blood pressure and class of antihypertensive agents
*Levey AS. Clinical evaluation of renal function. In: Greenberg A, Cheung AK, Coffmann TM, Falk RJ, Jennette JC. *Primer on Kidney Diseases.* 2nd ed. San Diego, Calif: Academic Press; 1998:21. Reprinted with permission.

vides multiple benefits. Specifically, the MDRD study equation[3]:

- has been derived based on GFR measured using an accepted method (urinary clearance of ^{125}I-iothalamate or traceable to an isotope dilution mass spectrometry (IDMS) reference method[7]), hence it estimates GFR rather than creatinine clearance.
- has been developed using rigorous statistical method with a large development and validation data base incorporating a diverse population with a variety of kidney diseases.
- estimates GFR adjusted for body surface area without requiring measurement of height, weight, or 24-hour urine collection.
- was developed in a study population of men and women with the inclusion of race as a variable, it and has been validated in a separate study of African Americans with kidney disease.
- is more accurate in individuals with low GFR (less than approximately 90 mL/min/1.73 m^2) than the Cockcroft–Gault equation and creatinine clearance (Figure 2).

Result Reporting

LabCorp reports eGFR results as follows:

- any value >60 mL/min/1.73 m^2 as a literal ">60"
- any value <60 mL/min/1.73 m^2 as the actual numeric, eg, "41"
- the reference interval is changed to 60–137 (males) 128 (females) mL/min/1.73 m^2
- all results <60 are flagged

Rationale for Reporting

- These changes reflect updated guidelines from the National Institute of Health, National Kidney Disease Education Program and should eliminate inconsistencies linked to the patient's health status and the eGFR result.
- Several studies have demonstrated that the eGFR underestimates renal function in apparently healthy individuals.[13]
- These studies concluded that the MDRD equation was not sufficiently validated in a normal population and was only derived from a population with CKD.
- Studies are presently underway to validate the equation in several populations of varying health status as well as in individuals with normal renal filtration.[13]
- Since the validation of the MDRD equation occurred in patients with CKD, eGFR results that approach 60 mL/min/1.73 m^2 or below, are accurate and do reflect diminished renal function.
- CKD can occur in patients with eGFR results >60 mL/min/1.73 m^2 if they exhibit persistent proteinuria.
- Thus, the report states: "**Note:** Persistent reduction in eGFR <60 mL/min/1.73 m^2 defines CKD. Patients with eGFR values ≥60 mL/min/1.73 m^2 may also have CKD if evidence of persistent proteinuria is present."

The NKDEP encourages clinical laboratories to communicate with health care providers—including pharmacies—about the clinical issues associated with serum creatinine results using methods that have calibration traceable to IDMS. In February 2007, the National Institute of Standards and Technology (NIST) released a new standard reference material (SRM 967) that will provide a practical reference material for use in establishing traceability to IDMS creatinine methods.[10]

Markers of Kidney Damage

Proteinuria is the most common marker of kidney damage. The screening for proteinuria in adults is measured using an albumin-specific dipstick or an albumin-to-creatinine ratio on a random (spot) urine sample. A routine dipstick is not sensitive enough to detect small amounts of urine protein. The NKF recommends the following criteria be applied when evaluating the tests in random urine samples for CKD.[3]

- Albumin-specific dipstick positive
- Albumin/creatinine ratio >30 mg/g
- Routine dipstick (total protein) >1+
- Protein/creatinine ratio >200 mg/g

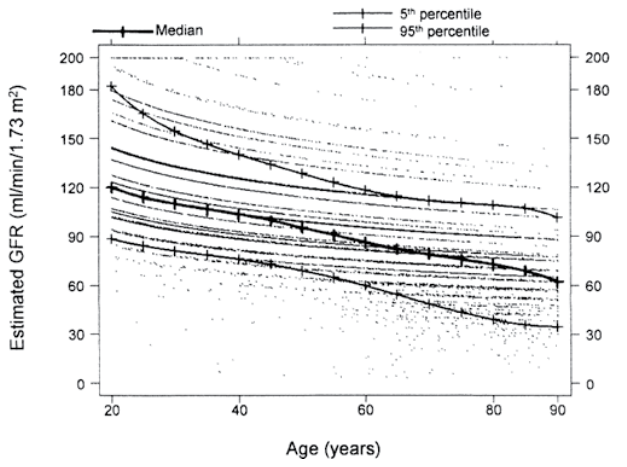

Figure 1. Percentiles of Estimated GFR Regressed on Age (NHANES III)

*National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. *Am J Kidney Dis.* 2002; 39 (Suppl 1):S1-S266. Reprinted with permission.[3]

Other markers of kidney damage may include the finding of RBCs and/or WBCs in urine sediment.

Serum Creatinine Measurements

As mentioned in the introduction, the serum creatinine concentration is affected by factors other than GFR, including creatinine secretion, generation, and extrarenal excretion.[3] Thus, there is a relatively wide range for serum creatinine in normal individuals, and GFR must decline to approximately half the normal level before the serum creatinine rises above the upper limit of normal. This is especially important in the elderly, in whom the age-related decline in GFR is not reflected by an increase in serum creatinine due to a concomitant age-related decline in creatinine production. Serum creatinine should be reported in addition to GFR estimates. While the serum creatinine result is a necessary component of the GFR formula, it should not be used alone to estimate the level of GFR without applying the MDRD study equation.

Creatinine Clearance Measurements

The level of creatinine clearance overestimates the level of GFR due to tubular secretion in addition to glomerular filtration of creatinine. In the MDRD Study, estimated GFR provided a more accurate estimate of measured GFR than measured creatinine clearance.[5] Thus, the NKF-K/DOQI guidelines do not recommend obtaining 24-hour urine collections for routine estimation of GFR. These collections are still useful for the indications listed in Table 5, as well as for assessment of diet and nutritional status, and the need to start dialysis.

Table 6. Clinical Situations in Which Clearance Measures May Be Necessary to Estimate Glomerular Filtration Rate (GFR)*

Extremes of age and body size
Severe malnutrition or obesity
Disease of skeletal muscle
Paraplegia or quadriplegia
Vegetarian diet
Rapidly changing kidney function
Prior to dosing drugs (with significant toxicity) that are excreted by the kidneys

*Levey AS. Clinical evaluation of renal function. In: Greenberg A, Cheung AK, Coffmann TM, Falk RJ, Jennette JC. *Primer on Kidney Diseases.* 2nd ed. San Diego, Calif: Academic Press; 1998:21. Reprinted with permission.

Limitations

The NKF-K/DOQI guidelines recognize limitations to estimating GFR from prediction equations and identify clinical conditions in which it may be necessary to measure GFR using clearance methods (Table 6).

- **Generalizability of the MDRD study prediction equation.** The MDRD study equation has not been validated in diabetic kidney disease, in patients with serious comorbid conditions, in normal individuals, or in individuals who are younger than 18[7] and older than 70. The equation also may not be accurate in patients at the extremes of body size or composition. Validation studies are in progress to evaluate the MDRD study equation for additional ethnic groups, the elderly, various disease conditions, and people with normal kidney function.[7]
- **Steady state assumptions.** GFR estimate can be interpreted only during a "steady state" of creatinine balance. GFR estimate will overestimate true GFR if serum creatinine is rising (such as in acute kidney failure) and will underestimate true GFR if serum creatinine is declining (as in resolution of acute kidney failure).[3]
- **False elevations of the serum creatinine concentration.** The serum creatinine concentration can be falsely elevated due to drug-induced inhibition of creatinine secretion, interference with the alkaline picrate assay for creatinine (Table 7), or creatinine supplementation.[3(pS80)] In these circumstances, GFR estimates will be falsely low. More accurate GFR estimates can be obtained by repeating the measurement of serum creatinine after discontinuation of the drug or resolution of the clinical condition.

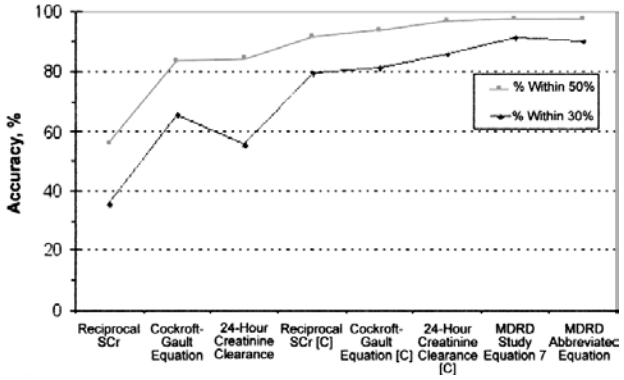

Figure 2. Accuracy of different estimates of GFR in adults, expressed as the percent of estimates within 30% and 50% of the measured GFR in the MDRD study validation sample.[3]

Table 7. Causes of Falsely Elevated Serum Creatinine Concentration*

- Drug-induced inhibition of creatinine secretion:
  - Trimethoprim
  - Cimetidine
- Interference with alkaline picrate assay for creatinine
  - Ketones and ketoacids
  - Some first-generation cephalosporins

*National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. *Am J Kidney Dis.* 2002; 39 (Suppl 1):S1-S266. Reprinted with permission.

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Estimated Glomerular Filtration Rate (eGFR) . . . 100768

Synonyms eGFR; GFR, Estimated;
Test Includes Creatinine, serum; eGFR calculation
Specimen Serum
Volume 1 mL
Minimum Volume 0.5 mL
Container Gel-barrier tube or transport tube
Collection Separate serum from cells within 45 minutes of collection.
Storage Instructions Maintain specimen at room temperature.
Causes for Rejection Hemolysis; improperly labeled specimen
Reference Interval
Male: 60.0-137.0 mL/minute
Female: 60.0-128.0 mL/minute
Note: The estimated GFR is multiplied by 1.212 in the cases of patients who are African American.
Limitations The equation is not applicable for pediatric patients, nor in those >70 years of age. The following conditions may alter the eGFR result: extremes in body size, severe malnutrition or obesity, skeletal muscle disease, paraplegia or quadriplegia, vegetarian diet, and rapidly changing kidney function.
Methodology Kinetic

For the most current information regarding test options, including specimen requirements and CPT codes, please consult the online Test Menu at www.LabCorp.com.

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