

Guideline for the Transition from the MDRD to the CKD-EPI Equation for the Calculation of an Estimated Glomerular Filtration Rate (eGFR), and its Interpretation in Concert with the Urine Albumin/Creatinine Ratio (ACR)**1. Purpose**

Ontario's community laboratories will soon be transitioning from the Modification of Diet in Renal Disease (MDRD) equation to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to calculate an eGFR. Recent literature indicates the CKD-EPI equation improves the accuracy of an eGFR. Interpretation of eGFR remains the same.

This Guideline identifies the benefits and limitations of the eGFR when calculated using the new equation. It also introduces the Kidney Disease Improving Global Outcomes (KDIGO) 2012 recommendation that the results of an eGFR should be interpreted in concert with the patient's ACR.¹ KDIGO is a global organization developing and implementing evidence-based clinical practice guidelines in kidney disease.

2. Background

Since 2006, Ontario's community laboratories have calculated and reported an eGFR when a serum creatinine was requested for individuals 18 years and older. Calculation of an eGFR is currently based on the MDRD equation. There is consensus that an eGFR represents the best routinely available measurement of kidney function.² The benefit of reporting an eGFR outweighs the limitations noted below.

The MDRD equation has been criticized as it underestimates the eGFR for those in a healthy population with serum creatinine at the upper limit of normal. This has led to an increased number of patients being classified as having stage 3 Chronic Kidney Disease (CKD) and over-diagnosis of CKD, particularly in women and the elderly.³

3. Benefits of the New CKD-EPI Equation

More recently, a modified equation has been endorsed by KDIGO, by the Canadian Society of Nephrology (CSN), and the Ontario Renal Network (ORN). The CKD-EPI equation is considered to be more accurate than the MDRD equation for calculating eGFR, particularly for patients with an eGFR in the 60-120 mL/min/1.73 m² range, for females, and for younger patient populations. The CKD-EPI equation uses a more sophisticated calculation for the eGFR, but includes the same factors as MDRD equation; those are age, gender, serum creatinine, and ethnicity. No additional patient information needs to be provided by clinicians.

A meta-analysis of eGFRs published in 2012 reviewed the outcomes from approximately 1.1 million patients, including a review of 25 general populations, 7 high-risk populations, and 13 CKD cohorts.⁴ When the CKD-EPI equation was used instead of the MDRD equation for calculation of the eGFR, approximately 24% of the general population patients were reclassified to a lower risk category, while 0.6% were reclassified to a higher risk category with

accompanying adverse outcomes. The majority of those reclassified to a lower risk category were younger, female, non-African descent patients with few risk factors and a lower rate of mortality.^{4, 5} Patients reclassified to a higher risk category were generally older with a mean age of 77 years. There is however, no single biomarker that meets all of the criteria for the ideal marker for routine determination of glomerular filtration rate. Both the MDRD and CKD-EPI equations rely on serum creatinine, as the indicator for the rate of glomerular filtration. Since serum creatinine correlates with both muscle mass and nutritional status, both equations suffer from the same limitations.⁶

Most studies have concluded that the CKD-EPI equation is more accurate than the MDRD equation for the calculation of an eGFR, but acknowledge that it does not work well for all patient populations.⁷⁻¹⁵ Studies suggest that use of the CKD-EPI equation predicts clinical risk more accurately for those of Asian descent and equally well for black populations.^{4, 15}

The new CKD-EPI calculation does not improve estimation of GFR in the renal transplant patient population.¹⁶

4. New Classification of CKD

The previous Kidney Disease Outcomes Quality Initiative (KDOQI) classification of CKD was based only on the eGFR. The realization that albuminuria is an independent predictor of cardiovascular mortality and morbidity and end stage renal disease, led to inclusion of albuminuria categories in the new classification scheme. The new classification of CKD is based on cause, the eGFR category, and albuminuria category (measured by ACR).^{1, 17} The table on the next page provides the classification of CKD, as per KDIGO 2012.¹

Note: Most patients with CKD will die of cardiovascular causes rather than end stage renal disease. Therefore it is important to focus on cardiovascular issues in all patients with CKD.¹⁸

5. Diagnosis and Monitoring of CKD by the eGFR and the ACR

CKD is defined in KDIGO 2012 as an abnormality of the kidney structure or function, which is present for more than 3 months, with implications for the patient's health.¹ Patients at high risk for CKD include those with clinical conditions, such as diabetes, hypertension, and those with a family history of kidney disease. The identification of the root cause for impaired renal function is important for the development of a patient management plan. A diagnosis of CKD is confirmed when:

- The eGFR is less than 60 mL/min/1.73 m², if duration exceeds 3 months.
- The ACR is equal to or greater than 3 mg/mmol creatinine, determined on 2 of 3 samples collected at least 3 months apart.

The KDIGO 2012 guideline highlights the importance of using both the eGFR and the ACR, expressed as the ratio of urine albumin to creatinine, in screening, diagnosis, and management of CKD.

The CSN supports routine reassessment of the eGFR and the ACR at clinically relevant intervals. Analysis should be repeated more often in patients with lower eGFR's, and/or with elevated baseline ACR's, and when rapid deterioration of renal function is suspected. Further, kidney function should be determined when prescribing medications that are influenced by kidney function. The CSN also recommends quantitation of ACR at diagnosis, to determine etiology of new onset edema and when changing therapy.¹⁷

The Canadian Diabetic Association (CDA) guidelines suggest screening patients with type 2 diabetes for CKD at diagnosis. Screening for CKD in patients diagnosed with type 1 diabetes

may be delayed for up to 5 years. Annual assessment of the eGFR and the ACR is recommended thereafter for all patients with diabetes.¹⁹

A random ACR from an early morning urine specimen is the recommended alternative to a timed urine albumin measurement and avoids the inherent collection issues associated with a 24-hour urine collection.¹⁷ Given the high biological variation for ACR and potential for other pathological or physiological explanations for an increased ACR, it is important to assess ACR when the patient is clinically stable. KDIGO recommends confirmation of a random urine ACR equal to or greater than 3 mg/mmol creatinine with a repeat analysis performed on an early morning specimen.¹

Note: For patients who do not have muscle mass typical of their demographic group, a 24-hour urine creatinine clearance may be used to improve diagnostic accuracy.

Prognosis of CKD by the eGFR and Albuminuria

Prognosis of CKD by the eGFR and ACR Categories: KDIGO 2012				Persistent Albuminuria (measured as ACR) Categories		
				Description and Range		
				A1	A2	A3
				Normal to mildly increased <3 mg/mmol creatinine	Moderately increased 3-30 mg/mmol creatinine	Severely increased >30 mg/mmol creatinine
eGFR Categories (mL/min/1.73 m ²) Description and Range	Category		eGFR			
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD);

Yellow: moderately increased risk; Orange: high risk;

Red: very high risk.

Adapted from KDIGO 2012 Kidney International Supplements. 2013;3; 1-150.

6. Limitations

Some limitations of the eGFR determined by CKD-EPI equation remain the same as eGFR determined by the MDRD equation. These include:

- True GFR is not reliably predicted by eGFR in vegetarians, amputees, for those at extremes of weight and age, and for those with a sudden change in GFR.
- Some medications, including trimethoprim, ciprofloxacin, and fenofibrate can increase serum creatinine, causing eGFR to underestimate true GFR.
- Neither the MDRD nor the CKD-EPI eGFR equation has been validated for patients who are pregnant or those less than 18 years of age.

Clinicians are reminded:

- Standard medication dosing guidelines for those with impaired renal function require the use of a calculated creatinine clearance, not an eGFR.
- For patients of African descent, the reported eGFR value should be multiplied by 1.15.
- eGFRs less than 60 mL/min/1.73 m² should be confirmed by repeat testing.
- CKD is documented by persistence of an eGFR less than 60 mL/min/1.73 m² for three months or longer and an ACR that is greater than or equal to 3 mg/mmol creatinine determined on 2 of 3 samples collected at least 3 months apart.^{1, 17}

7. Specialist Referrals

CSN recommends referral to a nephrologist in the following situations:¹⁷

- a. Acute renal failure;
- b. eGFR less than 30 mL/min/1.73 m²;
- c. Persistent albuminuria (ACR greater than or equal to 60 mg/mmol creatinine) or proteinuria (greater than or equal to 100 mg/mmol creatinine or greater than 1 g/day);
- d. Progressive loss of kidney function;
- e. Urinary red blood cell (RBC) casts, RBC greater than 20 per high power field, not readily explained;
- f. Persistent abnormalities of serum potassium;
- g. Recurrent or extensive nephrolithiasis;
- h. Polycystic kidney disease;
- i. Hereditary kidney disease;
- j. Unexpected or unexplained low eGFR or change in the eGFR (greater than 20%) especially in the non-elderly after excluding reversible causes and pre-renal azotemia;
- k. Inability to achieve targets for blood pressure or other renal or cardiovascular protective strategies, or if the clinician is unprepared to manage the CKD patient;
- l. Uncertainty about the diagnosis.

To Learn More

Please visit the OAML website's eGFR FAQ at <http://www.oaml.com/eGFR/faqs.html>

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