COLLEGE of AMERICAN PATHOLOGISTS

Chronic Kidney Disease Testing – Clinician Handout

SYNOPSIS AND RELEVANCE

Chronic kidney disease (CKD), among the most impactful disease states in the United States, results in significant morbidity and mortality, and is especially frequent in patients with chronic diseases such as hypertension and diabetes mellitus. Late identification results in a delay of focused treatment and decreases the chance for a timely renal transplant. Pathologists must be aware of the methods to diagnose and monitor the progression of CKD. Recent guidelines on CKD classification by the Kidney Disease: Improving Global Outcomes (KDIGO) organization, an international CKD working group,[1] and the College of American Pathologists[2] rely on consistent monitoring of estimated glomerular filtration rate (eGFR) and albuminuria (determined as the albumin-to-creatinine ratio [ACR]) for early identification and treatment. The National Kidney Foundation recommends the race-free 2021 CKD-EPI eGFR equation, which removed race from the calculations to enhance early recognition of CKD, especially in the African American population.

BACKGROUND

Chronic kidney disease (CKD) is a common condition that is recognized throughout the world. CKD has a high prevalence among adults worldwide at 10%, which increases up to 50% in high-risk populations.[3] Early recognition is paramount, as earlier stages of CKD are commonly asymptomatic and only uncovered via workup and laboratory testing driven by other comorbidities. The downstream implications are immense, as early disease may be reversible while late recognition and diagnosis lead to kidney failure. An understanding of CKD screening, diagnosis, and monitoring is imperative to promote appropriate and effective laboratory test utilization. Rates of proper screening remain low, as 80% of patients with diseases such as diabetes and/or hypertension do not receive a guideline-compliant laboratory assessment.[4]

Modern laboratory-based definitions for CKD and recommendations for screening by laboratory testing are sourced from the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.[1] The definition of CKD is greater than (>) 3 months of abnormalities of kidney structure or function. Classification of CKD by laboratory methods is predominantly based on two laboratory parameters: eGFR and albuminuria, determined by the albumin-to-creatinine ratio (See **Appendix A**). The categories stratify risk of progression, and are classified as low-, moderate- and high-risk. The introduction of the test ordering panel, “Kidney Profile,” an order set containing eGFR and ACR, may be a means by which the laboratory may promote complete kidney function screening using both tests.[2]

Glomerular filtration rate (GFR) is utilized to determine the amount of blood passing through the kidneys per minute, and primary routine monitoring is via the eGFR. Laboratories calculate the eGFR by multiple methods such as the Modification of Diet in Renal Disease (MDRD) equation[3] or analogs, such as creatinine clearance, however, the CKD-EPI equation[6] is recommended for adults because it allows more accurate stratification of early kidney disease (Stages 1 and 2). Pediatric eGFR is determined by the Schwartz Equation[3]; however, routine screening via calculation of eGFR is not recommended in children.

In 2021, the CKD-EPI equation was redesigned to address the large racial bias in the recognition of CKD.[6] As race categorization can be subjective from the clinical team and/or the patient themself, the accuracy of non-biological racial mathematical modification has been questioned. The 2021 CKD-EPI refit equation removes the non-biological racial mathematical modification and updates the constants in the remainder of the equation.[5] This new equation is designed to identify earlier stages of CKD for all patients and thus identify candidates for kidney transplantation more rapidly, leading to better outcomes.

Of note, race-related complications are not the only population-based issue for kidney function laboratory test results; hormones for transgender treatment have effects on creatinine and cystatin C levels, and thus the eGFR.[1] Evaluation of muscle mass, sex assigned at birth, and gender identity should be considered when evaluating eGFR for CKD in transgender or non-binary populations.

The eGFR formulas use creatinine and/or cystatin C. As eGFR is highly dependent on creatinine measurement, careful consideration of the method and instrument is needed, especially if using the Jaffe method.[7] Both the enzymatic and Jaffe methods are considered acceptable, because both methods must be calibrated to be traceable to the Isotope Dilution Mass Spectrometry (IDMS) standard, and all analytical interferents for the methods, such as high bilirubin or glucose, beta-hydroxybutyric acid, and many drugs such as cephalosporins and dobutamine must be understood. However, the Jaffe chemical method is simply much more susceptible to the above interferences, despite modifications.

Calculating eGFR solely via creatinine concentrations may underestimate CKD so that cystatin C is an alternative to creatinine. Cystatin C is not reabsorbed from the renal tubule; thus its level is more directly proportional to the GFR. The CKD-EPI eGFR equation that uses both creatinine and cystatin C is more accurate than the creatinine-based equation alone when comparing eGFR versus measured GFR.[2] Adding cystatin C assessment has advantages, as in one study 16% of patients were correctly identified as having CKD by assessing cystatin C or albumin-to-creatinine ratios in addition to the creatinine eGFR results, which appeared to be normal.[8] When interferents to creatinine methods are present, or the creatinine-based eGFR is near a clinical decision point, use of cystatin C-based eGFR or a creatinine/cystatin C-based eGFR is advised. However, we need to address that systemic inflammation, adiposity, thyroid disease, and steroid use are recognized as non-GFR determinants of Cystatin C.

Proteinuria in the setting of hypertension or diabetes is an early marker of kidney disease. An initial assessment of proteinuria commonly uses the urine albumin-to-creatinine ratio (ACR) or, less commonly now, the urine protein-to-creatinine ratio (PCR). Early morning urine specimens are preferred[9]; however, spot urine can also be utilized as it correlates well with results from 24-hour collections in adults. Persistent albuminuria is defined as two positive tests over 3 months. The lower limit of quantitation for albumin on some instruments may limit the categorization of CKD, so note the analytical sensitivity of the methods used. The specification for the laboratory's albumin method should be reviewed and methods with a lower limit of quantitation (LLOQ) higher than clinical decision limits should not be used.

INSIGHTS

- Primary screening for Chronic Kidney Disease should always include an eGFR and urine albumin-to-creatinine Ratio (ACR).
- Laboratory eGFR calculations should use the race-free 2021 CKD-EPI creatinine formula, as recommended by the College of American Pathologists.
- When possible, use the version of the eGFR 2021 CKD-EPI calculation that includes a combination of cystatin C and creatinine.
- The Kidney Profile, a test order set that combines the urine albumin-to-creatinine ratio and eGFR, can be added to the laboratory test menu to improve compliance with effective CKD screening.
- Adding cystatin C to the in-house test menu will enable the use of the 2021 CKD-EPI creatinine/cystatin C equation which is the most highly recommended version by the NKF and CAP.

APPENDIX A

Current Chronic Kidney Disease (CKD) Nomenclature

KDIGO defines CKD as abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health. CKD is classified based on Cause, Glomerular filtration rate (GFR) category (G1–G5), and Albuminuria category (A1–A3).[1]

KDIGO: Prognosis of CKD by GFR and albuminuria categories

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	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. GFR, glomerular filtration rate.

Reference: KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International (2024) 105 (Suppl 4S), S117–S314. doi:10.1016/j.kint.2023.10.018

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