JAMA Clinical Guidelines Synopsis

Classification and Risk Assessment of Chronic Kidney Disease

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GUIDELINE TITLE KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

DEVELOPERS Kidney Disease: Improving Global Outcomes (KDIGO)

RELEASE DATE March 13, 2024

PRIOR VERSION 2012

TARGET POPULATION Adults and children with chronic kidney disease (CKD) who have not progressed to dialysis or kidney transplant

MAJOR RECOMMENDATIONS

- Validated glomerular filtration rate (GFR) estimating equations such as the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or the European Kidney Function Consortium (EKFC) equation to derive GFR from serum filtration markers are recommended, rather than relying on serum creatinine or cystatin C in isolation (1D).
- For diagnosis and staging of CKD, equations for estimating GFR (eGFR) that include both creatinine and cystatin C afford the greatest accuracy (1C).
- For patients with CKD GFR categories G3 to G5, use of an externally validated risk equation, such as the Kidney Failure Risk Equation to estimate the 2- and 5-year risks of kidney failure or the Z6 model to estimate the annual risk of kidney failure for years 1 through 4 after presentation, is recommended (1A).

Summary of the Clinical Problem

Chronic kidney disease is defined by decreased GFR or evidence of kidney damage based on but not limited to albuminuria, hematuria, and structural abnormalities present for at least 3 months. Whenever possible, an underlying cause should be established using serologic and imaging tests with consideration of genetic testing and percutaneous kidney biopsy, if necessary. Chronic kidney disease should be classified by GFR category (G1-G5) and albuminuria category (A1-A3). The threshold for a decreased GFR is less than 60 mL/min/1.73 m^2, which corresponds to GFR categories G3a to G5.[1] Glomerular filtration rate can be estimated using widely available biomarkers such as creatinine and cystatin C.[2] Herein, we focus on the laboratory measures of eGFR in CKD in adults and their use in risk assessment of kidney failure.[1]

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Characteristics of the Guideline Source

The guideline work group members had a wide range of expertise in kidney disease (**Table**). Recommendation strength was graded as level 1 (recommendations) or level 2 (suggestions) based on net benefits and harms, and certainty of evidence was rated from high (level A) to very low (level D).

Evidence Base

Randomized clinical trials and observational studies were included in the evidence review. Of the 6 recommendations about classification of CKD, 4 were level 1, of which 2 were based on A or B certainty of evidence.

Estimating GFR

The 2 most commonly used equations for eGFR are the CKD-EPI equation and the EKFC equation. Both equations include sex, age, serum creatinine, and serum cystatin C, but not race, and both have external validation showing that GFR estimated by creatinine and cystatin C ($eGFR_{cr\text{-}cys}$) is closer to measured GFR than estimates with either biomarker alone ($eGFR_{cr}$ or $eGFR_{cys}$).[1] A cohort study (6185 participants) compared $eGFR_{cr}$ and $eGFR_{cys}$ with GFR directly measured with iohexol clearance. The proportion of eGFR values within 30% of measured GFR (P_{30}) was reported for a variety of estimating equations. The equation that included both creatinine and cystatin C (CKD-EPI 2021) had the highest P_{30} at 86.4%, and the P_{30} was similar in subgroups of age, sex, and body mass index.[3]

Calculation of $eGFR_{cr\text{-}cys}$ is recommended in clinical situations in which $eGFR_{cr}$ is less accurate and when eGFR affects clinical decision-making. The $eGFR_{cr}$ is less accurate in patients with a body mass index of 40 or greater or with muscle mass changes (eating disorders, paraplegia, bodybuilding), certain diets (high- and low-protein diets), comorbidities (cancer, heart failure, cirrhosis), and certain medications (steroids; medications that decrease tubular creatinine secretion, such as trimethoprim and cimetidine).[1] A cohort study of 1200 patients with history of a solid malignancy (22.7% breast cancer, 21.8% prostate cancer, and 20.9% gastrointestinal cancer) and no recent cancer treatment compared GFR directly measured with ^{51}Cr-EDTA vs $eGFR_{cr}$ and $eGFR_{cr\text{-}cys}$.[4] The $eGFR_{cr}$ was less

Table. Guideline Rating[a]

Establishing transparency	Good
Management of conflict of interest in the guideline development group	Fair
Guideline development group composition	Good
Clinical practice guideline–systematic review intersection	Good
Establishing evidence foundations and rating strength for each of the guideline recommendations	Good
Articulation of recommendations	Good
External review	Good
Updating	Good
Implementation issues	Good

[a] Cifu AS, Davis AM, Livingston EH. Introducing JAMA Clinical Guidelines Synopsis. *JAMA*. 2014;312(12):1208-1209.

accurate (P_{30} = 81.9%; 95% CI, 78.8%-83.2%) than the $eGFR_{cr\text{-}cys}$ (P_{30} = 92.2%; 95% CI, 90.6%-93.7%).[4]

Risk Assessment in CKD

Studies have examined the correlation between eGFR and risk of adverse outcomes including progression of kidney disease, dialysis, and death. A meta-analysis of individual-level data examined the association of CKD stage and increasing albuminuria with a broad range of adverse outcomes among 27 503 140 participants from 114 global cohorts using $eGFR_{cr}$ and 720 736 participants from 20 cohorts using $eGFR_{cr\text{-}cys}$.[5] The risk of adverse outcomes increased with decreasing eGFR and increasing urine albumin level for all cohorts. For example, using an $eGFR_{cr}$ of 90 to 104 mL/min/1.73 m^2 and a urine albumin-creatinine ratio of less than 10 mg/g as the reference category, an $eGFR_{cr}$ of 45 to 59 mL/min/1.73 m^2 and a urine albumin-creatinine ratio of less than 10 mg/g was associated with an increased risk of all-cause mortality after adjustment for age, sex, smoking status, systolic blood pressure, and multiple other covariates (adjusted hazard ratio, 1.3; 95% CI, 1.2-1.4; median incidence, 51 per 1000 person-years; mean follow-up, 4.8 years).[5] However, for patients with the same eGFR, the $eGFR_{cr}$ underestimated mortality risk vs $eGFR_{cr\text{-}cys}$, which showed higher all-cause mortality (adjusted hazard ratio, 1.7; 95% CI, 1.5-1.8; mean follow-up, 10.8 years).[5] This discrepancy is attributed to non-GFR factors that affect cystatin C level, such as smoking, hyperthyroid or hypothyroid disease, chronic inflammatory conditions such as those associated with elevated C-reactive protein, or lower serum albumin.[1]

Validated risk equations are also helpful to estimate the absolute risk of kidney failure requiring dialysis or transplant in people with CKD categories G3 to G5. For example, the Kidney Failure Risk Equation was developed and initially validated in 8391 adults from 2 Canadian provinces and subsequently validated in 721 357 individuals from more than 30 countries (C statistic, 0.88-0.91).[1,6,7] The Z6 model is the only risk prediction tool that uses cystatin C and was highly accurate in 4 European cohorts (C statistic, 0.89-0.92),[1] but it has not been validated in other populations.

Benefits and Harms

Several effective therapies to slow progression of CKD are now available,[1] so more accurate assessment of eGFR should lead to improved identification and treatment of patients with CKD. In some patients, use of $eGFR_{cr\text{-}cys}$ may decrease harms from less accurate $eGFR_{cr.}$ For example, more accurate eGFR may be important when selecting doses of medications that have narrow therapeutic windows. In a cohort study of 1869 adults with cancer who had simultaneous creatinine and cystatin C measurements, 543 patients (29%) had an $eGFR_{cys}$ that was more than 30% lower than their $eGFR_{cr}$. These patients were more likely to have medication-related adverse events (such as supratherapeutic drug levels, hyperkalemia, or orthostatic hypotension) for kidney-cleared medications (vancomycin, trimethoprim-sulfamethoxazole, baclofen, and digoxin) compared with patients who had $eGFR_{cys}$ within 30% of $eGFR_{cr}$.[8]

Discussion

The guideline advises against inclusion of race in eGFR equations due to use of race as a binary variable and limited improvement in accuracy of the estimation when race is included. The 2 most commonly used equations for eGFR (CKD-EPI 2021 and EKFC) include age and sex but do not include race. The CKD-EPI 2021 equation, which uses both creatinine and cystatin C but not race, was associated with a P_{30} of more than 90% for Black and non-Black individuals, which supports the recommendation to exclude race as it is an unnecessary variable in eGFR models.[9] When evaluating patients who have varying eGFRs reported by different laboratories, the CKD-EPI equation and the EKFC equation can be used to evaluate whether the difference is attributable to $eGFR_{cr}$ vs $eGFR_{cr\text{-}cys}$.

Areas in Need of Future Study or Ongoing Research

Further study is needed comparing how eGFR, as determined by creatinine, cystatin C, or the combination, varies over time. Differences in eGFR over time may have implications regarding clinical decision-making for individual patients, as well as in decisions about eligibility criteria in clinical trial design.

ARTICLE INFORMATION

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Published Online: November 5, 2025. doi:10.1001/jama.2025.18457

Conflict of Interest Disclosures: None reported.

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