Cystatin C should be routinely available for estimating kidney function

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Purpose of review
In this report, we summarize why the availability of cystatin C is important across a variety of clinical scenarios, the recent literature on when, why and in whom cystatin C testing should be considered, and how nephrologists can take practical steps to incorporate cystatin C testing into their practice.

Recent findings
Large intra-individual discrepancies between estimated glomerular filtration rate by creatinine (eGFRcr) and estimated glomerular filtration rate by creatinine eGFRcys (known as eGFRdiff) are observed in at least 1 in 4 people. These differences are seen more commonly among more vulnerable individuals: older adults, females, non-White individuals and those living with multiple medical conditions. A large eGFRdiff, where eGFRcys is lower than eGFRcr, is associated with a plethora of adverse outcomes, including medication-associated adverse events, acute kidney injury, cardiovascular disease, kidney failure and all-cause mortality. Among studies that have measured GFR, eGFRcr-cys usually provides the most accurate estimation of kidney function compared to mGFR, including among participants with large discrepancies between eGFRcr and eGFRcys.

Summary
Cystatin C improves sensitivity and specificity of chronic kidney disease diagnosis, improves detection of harmful acute and chronic changes in kidney function, improves precision of treatment eligibility and safety, and may reduce healthcare inequalities. Better education, curiosity, and motivation among nephrologists could substantially improve the availability and utilization of cystatin C.

Keywords
chronic kidney disease, creatinine, cystatin C, estimated glomerular filtration rate

INTRODUCTION

Early epidemiological literature that compared estimated glomerular filtration rate by creatinine (eGFRcr), cystatin C (eGFRcys) or the combination of both markers (eGFRcr-cys) was predominantly focused upon equation performance at the population level. Estimates that incorporate cystatin C are better prognostic markers than eGFRcr, and align better with measured GFR (mGFR) in global populations [1–4,5▪▪,6]. However, aggregate findings from population studies have proven difficult to interpret for clinical practice. Implications for whom cystatin C testing would be most valuable were unclear.

Recently, several studies have evaluated situations where eGFRcr and eGFRcys are discrepant and described the prevalence and clinical implications of wide differences. In this report, we will summarize why we believe that availability of cystatin C is important across a variety of clinical scenarios, the recent literature that informs priorities for utilization of cystatin C testing, and how the nephrologist can take practical steps to incorporate cystatin C testing into their practice.

CYSTATIN C IMPROVES SENSITIVITY AND SPECIFICITY OF CRONIC KIDNEY DISEASE DIAGNOSIS

International guidelines state that the first step of CKD care is accurate diagnosis and staging: this

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KEY POINTS

- Around 1 in 4 individuals have eGFRcys that is lower than eGFRcr by at least 15 ml/min/1.73m^2
- At population level, and where wide discrepancies exist between eGFRcys and eGFRcr, eGFRcr-cys on average provides the most accurate estimate of kidney function.
- Cystatin C improves sensitivity and specificity to detect harmful acute and chronic changes in kidney function, and better identifies those at high risk of adverse outcomes associated with chroni kidney disease.
- Cystatin C improves the precision of treatment eligibility and safety; enhanced cystatin C testing may reduce the occurrence of medication-related adverse events.
- eGFRcr is more likely to be inaccurate in populations considered to be underserved – including individuals who are older, female, non-White, people living with multiple health conditions and continental African populations; enhanced cystatin C testing could reduce healthcare inequalities.

should therefore be a priority for optimal care [7]. The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines on CKD diagnosis and management [7], and *draft* guidelines to be published in February 2024, support the use of cystatin C for improved accuracy in diagnosis and staging.

Global population studies demonstrated that eGFR equations incorporating cystatin C improve accuracy compared to eGFRcr alone [1–4,5▪▪,6,8,10]. Common to all studies are two metrics which indicate the degree of precision and bias. Precision is usually assessed according to the percentage of individuals with estimates within 30% of mGFR (P30); 80–90% is considered acceptable, but P30 values greater than 90% are ideal. Bias is usually reported as the absolute difference between mGFR and eGFR, and larger mean differences indicate greater bias.

In nearly all studies, eGFRcr-cys had the best performance compared with mGFR, and eGFRcr was never the most precise or least biased. In the largest and most recent studies [2,4,11] from predominantly North American and European cohorts, precision and bias were best for eGFRcr-cys. In the largest dedicated study conducted in Sub-Saharan Africa, bias was minimized with eGFRcys though both eGFRcys and eGFRcr-cys offered similar precision [6].

However, these studies have not considered the clinical implications for individuals whose estimates provided by eGFRcr and eGFRcys disagree. Persons with large differences in eGFRcr and eGFRcys are characterized by adverse health characteristics when eGFRcys is lower and favorable health profiles when eGFRcys is higher (Fig. 1).

The largest study to date, from clinical data comprising around 158 000 adults with concurrent creatinine and cystatin C testing (SCREAM [12]), found that large individual discrepancies between eGFRcr and eGFRcys (known as eGFRdiff) were extremely common [13▪]. eGFRcys was lower on average compared with eGFRcr (mean difference: -8 ± 15 ml/min/1.73 m^2); 32% of individuals had lower eGFRcys by more than 15 ml/min/1.73 m^2 compared with eGFRcr [13▪]. Multiple epidemiological cohorts in North America, Europe and China have illustrated similar patterns, though with smaller absolute eGFR differences [14–17], likely reflecting differences in the populations under study. In the SCREAM analysis, people with larger eGFRdiff and lower eGFRcys were older, more likely to be female, and had higher prevalence of comorbidities and concomitant medications [5▪▪], all of which portend substantial potential for treatment inaccuracy and adverse events [13▪,18▪▪]. Importantly, large eGFRdiff with lower eGFRcys is common among individuals with eGFRcr >60 ml/min/1.73 m^2, which could lead to false reassurance and suboptimal monitoring for these individuals. In situations where eGFRcr and eGFRcys are highly discrepant, all studies with measured GFR have found that cystatin C testing, either as eGFRcys or eGFRcr-cys, improves accuracy [5▪▪,19].

CYSTATIN C IMPROVES DETECTION OF HARMFUL CHANGES IN KIDNEY FUNCTION

Risk stratification of future events

Across a variety of populations and different geographical areas, a single, baseline value of eGFRcys or eGFRcr-cys is better than eGFRcr for discriminating risk of future adverse events, including atherosclerotic cardiovascular disease, ischemic and hemorrhagic stroke, acute kidney injury, heart failure, kidney failure, cancer, and all-cause mortality [20–24]. Recently, in a study of 452 879 participants in the UK Biobank, eGFRcys more sensitively detected risk of first ischaemic stroke compared with eGFRcr in both male and female participants, but the effect was more pronounced among females [male adjusted hazard ratio (aHR) 1.16, 95% confidence interval (CI) 1.12–1.19; female to male comparison: aHR 1.11, 95% CI 1.05–1.16, per 10 ml/min/1.73 m^2 lower value of eGFRcys] [25]. It is plausible that cystatin C may offer enhanced risk stratification for other at-risk populations

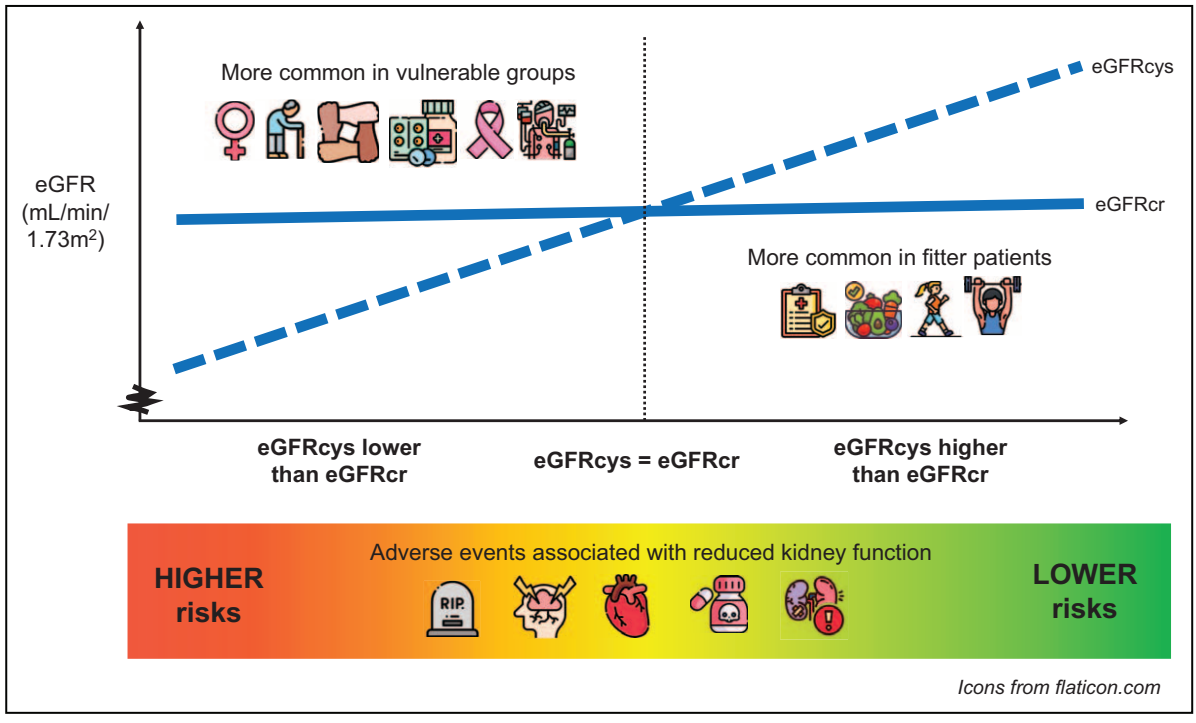

FIGURE 1. Infographic illustrating risk factors and adverse events associated with differences between eGFRcys and eGFRcr. Vulnerable groups include females, older people, members of non-White racial/ethnic groups, continental African populations, those who are frail, with multiple or serious long-term medical conditions (including, but not limited to cancer) and/or who are taking multiple medications and those who are critically ill. Adverse events can include acute kidney injury, progressive chronic kidney disease and kidney failure, medication-associated adverse events, cardiovascular disease, stroke and all-cause mortality. eGFR, estimated glomerular filtration rate.

where discrepancies between eGFRcr and eGFRcys are common.

Chronic kidney disease progression

With the passage of time – due to aging as well as critical illness – eGFRcr and eGFRcys often diverge, usually with a progressively lower eGFRcys relative to eGFRcr [19,26]. In the Chronic Renal Insufficiency Cohort (CRIC) study of 4956 patients in the United States with median follow-up 7.2 (interquartile range, IQI 4.4–9.7) years, longitudinal widening of eGFRdiff, eGFRcys decreasing faster than eGFRcr, was associated with higher mortality risk [27]. Compared with participants who had similar slopes by eGFRcys and eGFRcr, those with faster eGFRcys declines had an 8-fold adjusted mortality risk [hazard ratio (HR) 8.20, 95% CI 6.37–10.56], and those with larger apparent declines by eGFRcr had a substantially lower mortality risk (HR 0.14; 95% CI 0.08–0.24). In the same cohort, participants with faster declines in eGFRcys relative to eGFRcr also had higher risk of incident heart failure (HR 1.49, 95% CI 1.19–1.85) compared with those in whom eGFRcys and eGFRcr declined in parallel [28]. Thus, differential changes in eGFRcys and eGFRcr over time have potential to increase both the sensitivity and specificity for detecting clinically significant CKD progression relative to monitoring with eGFRcr alone.

Acute kidney injury

Widening eGFRdiff, characterized by lowering eGFRcys, may be observed even when eGFRcr is static or improving. This effect has been observed recently among 39, critically unwell, prospectively enrolled patients in the intensive care unit (ICU) [29▪▪]. In this group of relatively young and fit individuals with low levels of comorbidity, eGFRcr steadily rose following ICU admission from 79 (IQI 51–102) to 105 (IQI 97–122); meanwhile, eGFRcys fell from 78 (IQI 36–177) to 70 (IQI 37–99) ml/min/ 1.73 m^2. After a median length of stay 16.5 days), eGFRcr overestimated the median measured GFR of 58 ml/min by 59 (IQI 49–69) ml/min, in parallel with dramatic reductions in quadriceps muscle mass. This is concerning for two reasons: first, the loss of muscle mass indicates increasing sarcopenia with an artefactual rise in eGFRcr; second,

deteriorating eGFRcys indicates worsening kidney function. The combination of diverging eGFRcr-eGFRcys and lowering eGFRcys implies increased risk, as each is a risk factor for a plethora of adverse events, including death. When depending on creatinine as the sole marker of kidney function, neither of these concerns can be detected, to the detriment of clinical care for that patient.

In the Molecular Epidemiology of SepsiS in the ICU (MESSI) prospective cohort study, combination treatment with vancomycin and piperacillin-tazobactam was associated with higher rates of creatinine-defined acute kidney injury (rate ratio: 1.34, 9% CI 1–01–1.78) compared to vancomycin with cefepime. By comparison, vancomycin with piperacillin-tazobactam was not associated with changes in cystatin C nor with adverse clinical outcomes [30]. Dolutegravir, which blocks tubular secretion of creatinine, is used widely as first-line antiretroviral therapy and has been associated with significant early and sustained rises in serum creatinine over a 48-week treatment period [31]. Two recent reports [32,33] add to an expanding literature [34] describing cases where targeted systemic anticancer treatments lead to a rise in creatinine suggestive of acute kidney injury (AKI), in many cases leading to temporary or permanent cessation of treatment, and with major potential impacts on cancer progression and survival.

Across each of the scenarios described above, parallel increases in cystatin C were not observed, suggesting pseudo-AKI [30–34]. For drugs that competitively inhibit tubular creatinine excretion, use of creatinine alone makes it impossible to distinguish true AKI, potentially compromising clinical care. Changes in eGFRcr are therefore both less sensitive and less specific than eGFRcys for clinically significant changes in kidney function in many clinical settings.

CYSTATIN C IMPROVES THE PRECISION OF TREATMENT ELIGIBILITY AND SAFETY

Cystatin C has the potential to enhance our ability to choose the right treatments. In a study of 1839 patients with cancer and simultaneous recording of creatinine and cystatin C, 543 (29%) had eGFRcys that was more than 30% lower than eGFRcr [18▪▪]. Compared with patients who had similar eGFRcr and eGFRcys, these wide eGFRdiff patients were more likely to experience major medication-related adverse events: supra-therapeutic vancomycin (43/179 vs. 7/77; $P = 0.01$) and digoxin levels (7/24 vs. 0/10, $P = 0.08$), hyperkalemia associated with trimethoprim-sulfamethoxazole treatment (29/129 vs. 11/92, $P = 0.07$), and toxic effects of baclofen (5/19 vs. 0/11, $P = 0.19$). In a prospective quality improvement project in the ICU, a vancomycin dosing algorithm based on eGFRcr-cys, compared with Cockcroft-Gault creatinine clearance, substantially improved likelihood of obtaining therapeutic trough levels [odds ratio (OR) 2.53, 95% CI 1.65–3.90], which persisted after adjustment for other clinical and diagnostic parameters (adjusted OR 2.79, 95% CI 1.76–4.44) [35]. A systematic review of 28 articles (3455 participants), including major drugs and drug classes where renal elimination and nephrotoxicity are important (vancomycin, aminoglycosides, beta-lactams, digoxin, dabigatran and carboplatin) [36] reported consistent findings. Though eGFRcr-cys performed best overall, eGFRcys consistently outperformed eGFRcr for prediction of drug levels and drug clearance [36].

Cystatin C also improves treatment selection across clinically relevant thresholds. In 440 526 patients in the UK Biobank, eGFRcys improved classification of high cardiovascular risk across the threshold for statin treatment by 1.5% [21], a similar improvement in risk stratification as is afforded by inclusion of lipids. Importantly, this risk stratification is most effective among people with mild CKD, who would be unlikely to get referred to a nephrologist and would offer them appropriate primary prevention treatment. We are not aware of direct work to show enhanced eligibility assessment for other preventive therapies, but it is likely that more effective detection of mild CKD would enhance identification and eligibility for other medications known to reduce cardiometabolic risk and mortality, such as sodium-glucose co-transporter-2 (SGLT2) inhibitors.

CYSTATIN C COULD REDUCE HEALTHCARE INEQUALITIES

Wide discrepancies in eGFRcr and eGFRcys are more common in individuals who are older, female, non-White, people living with multiple health conditions and continental African populations. Unfortunately, these groups are already less likely to receive evidence-based treatments – including renin-angiotensin system inhibitors, statins and SGLT2 inhibitors [37–39] – that offer potential for substantial benefits [40,41] and referral into appropriate nephrology care – including transplant work-up and listing.

In a recent study of 637 potential living kidney donors in a single centre in the United States, misclassification of eGFRcr compared to mGFR across a threshold of 80 ml/min required for living kidney donation was around 16% for the whole population. Inappropriate donor exclusion varied by race and eGFR equation but was more likely among potential Black compared with White donors when using the

recommended CKD-EPI 2021 equation without race coefficient [42].

The National Kidney Foundation-American Society of Nephrology Task Force called for greater uptake of cystatin C testing [43], in part to lessen the race inequalities in kidney function estimation that are exacerbated by reliance on creatinine. Enhanced cystatin C testing would improve risk stratification, objective eligibility across treatment thresholds, dosing accuracy and tolerability of treatments to a greater degree in underserved groups where creatinine-based measures are less likely to be accurate.

THE MAJOR REASONS NOT TO TEST CYSTATIN C ARE EXCUSES

Cystatin C is more expensive than creatinine

Cost differences between creatinine and cystatin C depend largely upon volume of use. In Sweden, a major public health drive in utilizing cystatin C since its discovery has allowed cystatin C to be widely available with equivalent cost to creatinine. In a San Francisco (California, United States) hospital, cystatin C costs USD 5, but at low volumes, testing would be more expensive due to higher overheads in paying for reagent batches that would expire without at least mild routine use. Clinicians may argue that cystatin C testing is not feasible due to the higher costs relative to creatinine. Considering the frequency of use, cystatin C testing would be less expensive than many or most routine tests and procedures in nephrology.

Cystatin C is not available

Most places have access to cystatin C testing somewhere, even if not in the nearest laboratory. In the United States, cystatin C is available through commercial laboratories (e.g., Labcorp, Quest). In the United Kingdom, testing is available in London, and soon will be available in Glasgow. In Africa, cystatin C is available in private healthcare settings. Importantly, cystatin C testing is a simple chemical assay, and with motivated clinical teams, is uncomplicated to bring in-house. All common automated analyzer equipment in the chemistry laboratory has the capacity to measure cystatin C.

External quality assessment is not validated for cystatin C

Recommendations to standardize laboratory creatinine were made in 2006 [44]. To date, many laboratories across low-, middle- and high-income countries have not implemented the recommendations (e.g., persisting use of Jaffe rather than enzymatic creatinine), but we still use creatinine as our primary biomarker to estimate kidney function. Major vendors for cystatin C have excellent standardization, international reference material is available, and external quality assessment programmes exist [45]. Despite evidence of utility, the final decisions across most settings relate to cost or clinical inertia.

WE STRONGLY SUPPORT ROUTINE AVAILABILITY OF CYSTATIN C TESTING FOR ESTIMATING KIDNEY FUNCTION

In making this statement, we wish to highlight some further considerations. First, we are convinced of the potential utility of cystatin C among adult populations with nondialysis CKD, among whom the data are most abundant and robust. We consider that there are too few data to provide a clear position in paediatric population and adults with kidney failure (including kidney transplant). Second, we do not contend that cystatin C should always be used in all patients for kidney function estimation, but simply that it must be available in all settings. As we learn more about the patients and clinical scenarios where cystatin C testing adds greatest value, guidance will become clearer. This has major implications for the concerns around costs, where measurement costs can be balanced through the efficiencies of increased testing volumes and judicious use among patients most likely to benefit. Third, most testing currently (for both creatinine and cystatin C) is conducted within laboratory facilities. Point-of-care testing offers an alternative that may have a modest reduction in precision but may improve diagnosis in some hard-to-reach communities and populations. Fourth, calibration of GFR estimating equations to the population under study can improve the performance within individual populations, though previous analyses suggest a much greater influence of the selected biomarker than the equation on the estimates provided [11]. We have therefore not undertaken any detailed comparisons among the GFR estimating equations that utilize cystatin C.

Outside nephrology, risk markers are continually being updated and refined. In the time that nephrologists have persisted with creatinine, cardiologists have progressed from creatine kinase through increasingly sensitive troponin tests to support a diagnosis of myocardial infarction, and have provided evidence that thresholds should be sex-specific. Meanwhile, we use creatinine to estimate our most important metric, which provides wildly inaccurate results in at least 1 in 4 of our most vulnerable patients [5▪▪,11].

CONCLUSION

To overcome the inertia in testing cystatin C more widely, we recommend that nephrologists rediscover the curiosity and fastidiousness that is associated with the specialty and follow these four steps. First, recognize and acknowledge the potential benefits of cystatin C testing from a public health perspective; encourage and educate colleagues where necessary. Second, accept that there will be some uncertainty in estimates provided and learn how to exercise clinical judgement in their interpretation. Third, take direct, individual action to engage with the local laboratory to identify and implement an effective route to cystatin C testing. Finally, when treating one of the many patients with characteristics associated with increased or decreased creatinine production, consider whether there is a justifiable reason not to order one additional test [9].

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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This study included 6,185 adults with 9,404 concurrent measurements of measured GFR by iohexol clearance, creatinine and cystatin C from the Stockholm CREAtinine Measurements project (SCREAM). The authors found that large discrepancies between eGFRcr and eGFRcys were common, and in these settings, eGFRcr-cys usually provided the most accurate estimate of GFR. These findings were consistent on average among people with comorbidities including cardiovascular disease, heart failure, diabetes, liver disease and cancer.

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