

RESEARCH ARTICLE

The clinical utility and cost impact of cystatin C measurement in the diagnosis and management of chronic kidney disease: A primary care cohort study

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Abstract

Background

To reduce over-diagnosis of chronic kidney disease (CKD) resulting from the inaccuracy of creatinine-based estimates of glomerular filtration rate (GFR), UK and international guidelines recommend that cystatin-C-based estimates of GFR be used to confirm or exclude the diagnosis in people with GFR 45–59 ml/min/1.73 m² and no albuminuria (CKD G3aA1). Whilst there is good evidence for cystatin C being a marker of GFR and risk in people with CKD, its use to define CKD in this manner has not been evaluated in primary care, the setting in which most people with GFR in this range are managed.

Methods and findings

A total of 1,741 people with CKD G3a or G3b defined by 2 estimated GFR (eGFR) values more than 90 days apart were recruited to the Renal Risk in Derby study between June 2008 and March 2010. Using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, we compared GFR estimated from creatinine (eGFR_{creat}), cystatin C (eGFR_{cys}), and both (eGFR_{creat-cys}) at baseline and over 5 years of follow-up. We analysed the proportion of participants with CKD G3aA1 reclassified to ‘no CKD’ or more advanced CKD with the latter two equations. We further assessed the impact of using cystatin-C-based eGFR in risk prediction equations for CKD progression and all-cause mortality and investigated non-GFR determinants of eGFR_{cys}. Finally, we estimated the cost implications of implementing National Institute for Health and Care Excellence (NICE) guidance to use eGFR_{cys} to confirm the diagnosis in people classified as CKD G3aA1 by eGFR_{creat}. Mean eGFR_{cys} was significantly lower than mean eGFR_{creat} (45.1 ml/min/1.73 m², 95% CI 44.4 to 45.9, versus 53.6 ml/min/1.73 m², 95% CI 53.0 to 54.1, *P* < 0.001). eGFR_{cys} reclassified 7.7% (50 of 653) of those with CKD G3aA1 by eGFR_{creat} to eGFR ≥ 60 ml/min/1.73 m².

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Abbreviations: AUROC, area under the receiver operating characteristic curve; BMI, body mass index; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; creat, creatinine; creat-cys, creatinine and cystatin C; CVD, cardiovascular disease; cys, cystatin C; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; GP, general practitioner; hsCRP, high-sensitivity C-reactive protein; KDIGO, Kidney Disease Improving Global Outcomes; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; RRID, Renal Risk in Derby; SBP, systolic blood pressure; uACR, urine albumin-to-creatinine ratio.

However, a much greater proportion (59.0%, 385 of 653) were classified to an eGFR category indicating more severe CKD. A similar pattern was seen using eGFR_{creat-cys}, but lower proportions were reclassified. Change in eGFR_{creat} and eGFR_{cys} over 5 years were weakly correlated ($r = 0.33$, $P < 0.001$), but eGFR_{cys} identified more people as having CKD progression (18.2% versus 10.5%). Multivariable analysis using eGFR_{creat} as an independent variable identified age, smoking status, body mass index, haemoglobin, serum uric acid, serum albumin, albuminuria, and C reactive protein as non-GFR determinants of eGFR_{cys}. Use of eGFR_{cys} or eGFR_{creat-cys} did not improve discrimination in risk prediction models for CKD progression and all-cause mortality compared to similar models with eGFR_{creat}. Application of the NICE guidance, which assumed cost savings, to participants with CKD G3aA1 increased the cost of monitoring by £23 per patient, which if extrapolated to be applied throughout England would increase the cost of testing and monitoring CKD by approximately £31 million per year. Limitations of this study include the lack of a measured GFR and the potential lack of ethnic diversity in the study cohort.

Conclusions

Implementation of current guidelines on eGFR_{cys} testing in our study population of older people in primary care resulted in only a small reduction in diagnosed CKD but classified a greater proportion as having more advanced CKD than eGFR_{creat}. Use of eGFR_{cys} did not improve risk prediction in this population and was associated with increased cost. Our data therefore do not support implementation of these recommendations in primary care. Further studies are warranted to define the most appropriate clinical application of eGFR_{cys} and eGFR_{creat-cys}.

Author summary

Why was this study done?

- Estimation of kidney function (glomerular filtration rate) from serum creatinine concentration may be inaccurate in some people due to the impact of muscle mass, diet, and drugs on creatinine concentration.
- To reduce over-diagnosis of chronic kidney disease, international and UK guidelines recommend that the diagnosis of chronic kidney disease should be confirmed with an estimate of kidney function based on a different marker of glomerular filtration, cystatin C, in those people with only a mild reduction in glomerular filtration rate and no albuminuria.
- The clinical utility of this guidance has not been adequately evaluated in primary care, the setting in which most people with chronic kidney disease are cared for.

What did the researchers do and find?

- We estimated glomerular filtration rate from serum creatinine and cystatin C in a cohort of 1,741 mainly older people diagnosed with chronic kidney disease in primary care.

- The use of cystatin C to confirm a diagnosis of chronic kidney disease resulted in reclassification of a small proportion (7.7%) of people as not having chronic kidney disease, but a much greater proportion were reclassified as having more advanced disease (59%).
- In this cohort, the use of cystatin C did not result in improved risk prediction for all-cause mortality or progression of chronic kidney disease.
- We estimate that the use of cystatin C as recommended in current guidelines would result in increased healthcare costs of £23 per person in the first year of implementation.

What do these findings mean?

- Our data do not support the use of cystatin C to confirm a diagnosis of chronic kidney disease in primary care.
- Cystatin C may be useful for estimating glomerular filtration rate in other settings where creatinine is known to be unreliable, for example in people with extremes of body habitus.

Introduction

The use of serum creatinine concentration to estimate glomerular filtration rate (GFR) has become widely adopted as the principal test for the diagnosis of chronic kidney disease (CKD). However, the dependence of serum creatinine on muscle mass and the tendency of creatinine-based equations to underestimate GFR at values close to the diagnostic threshold of 60 ml/min/1.73 m² has raised concerns about the risk of over-diagnosis in otherwise healthy older populations when relying on this method and has prompted calls to identify more reliable endogenous filtration markers for the estimation of GFR [1]. Concern has also been expressed that the use of GFR estimated from creatinine but not corrected for age may result in under-diagnosis of CKD in younger people [2]. Cystatin C, a protein that normally crosses the glomerular filtration barrier, has been proposed as an alternative endogenous marker. Cystatin C is produced by all nucleated cells, and is therefore less influenced by muscle mass than creatinine [1,3,4]. Though estimation of GFR from cystatin C alone was found to be no more accurate than creatinine, estimated GFR (eGFR) derived from a combined creatinine and cystatin C equation was more accurate and showed greater precision than eGFR derived from creatinine or cystatin C alone [5].

National Institute for Health and Care Excellence (NICE) and Kidney Disease Improving Global Outcomes (KDIGO) guidance for the diagnosis of CKD stage 3 have recommended use of cystatin-C-based eGFR to confirm or exclude a diagnosis in those found to have a creatinine-based eGFR between 45 and 59 ml/min/1.73 m² and no albuminuria (CKD G3a1) [6,7]. However, the clinical impact and cost of implementing this recommendation has not been adequately evaluated in the population in which it will be applied: those with mildly reduced eGFR, managed predominantly in primary care. This is important because this group represents the majority of people defined as having CKD. Population-based studies have reported that 3.6% of adults in the US [8] and 3.2% of adults in the UK are in CKD stage G3a1 [9]. Additionally, whilst cystatin C is not dependent on muscle mass, it has been reported to have

other non-GFR determinants including sex, inflammation, obesity, diabetes, smoking, and thyroid dysfunction that may adversely affect GFR estimation in some populations [10–14].

Cystatin C has also been shown to improve discrimination in equations to predict adverse outcomes in CKD stage 3 including end-stage kidney disease (ESKD) [15], all-cause mortality [15], and cardiovascular mortality [16]. Potentially, therefore, its use in the diagnosis and continuing evaluation of people with CKD in primary care may improve our ability to detect individuals at high risk of adverse outcomes, to facilitate targeted monitoring and intervention including early referral to a nephrology service [17]. However, as yet there is little published evidence regarding the use of cystatin-C-based estimates of GFR for risk assessment in primary care.

In this analysis, we aimed to assess the impact of use of cystatin-C-based and combined creatinine and cystatin C eGFR compared to standard creatinine-based estimates in a primary care population with baseline CKD stage 3, defined by 2 measures of GFR more than 90 days apart, and to evaluate the non-GFR determinants of cystatin-C-based eGFR. Additionally, we compared creatinine- and cystatin-C-based estimates of GFR over 5 years of follow-up and evaluated the prognostic accuracy of cystatin C in risk prediction. Finally, we evaluated the cost implications of implementing NICE guidance to confirm a diagnosis of CKD G3a1 based on creatinine eGFR ($eGFR_{creat}$) by checking cystatin C eGFR ($eGFR_{cys}$) and also considered the use of creatinine and cystatin C eGFR ($eGFR_{creat-cys}$) as an alternative strategy.

Methods

Ethics

The Renal Risk in Derby (RRID) study was approved by the Nottingham Research Ethics Committee 1, and is included in the National Institute for Health Research Clinical Research Network Portfolio (NIHR Study ID. 6632). All participants provided written informed consent at study baseline, and repeated the consent at the year 5 study visit. The RRID study complies with the Declaration of Helsinki and the principles of good clinical practice.

Participants

Detailed methods for the RRID study have been published previously [18]. The study protocol and STROBE and STARD checklists are also available ([S1 Protocol](#); [S1 STROBE Checklist](#); [S1 STARD Checklist](#)). In all, 1,741 participants were individually recruited and prospectively studied from 32 Derbyshire primary care practices between June 2008 and March 2010. To start, 8,280 people were invited from practice registers of patients with CKD stage 3. Of these, 1,822 people attended baseline visits. All participants were aged over 18 years. Participants were selected using the 4-variable Modification of Diet in Renal Disease (MDRD) equation modified for use with isotope dilution mass spectrometry–standardised creatinine measurement. Two MDRD eGFR results consistent with CKD stage 3 ($30\text{--}59\text{ ml/min/1.73 m}^2$) more than 90 days apart were required to be eligible. People who were judged to have a life expectancy of less than 1 year, were unable to attend study visits at their primary care surgery, or had previously received a solid organ transplant were excluded from the study. Of the 1,822 people who attended baseline visits, 1,741 were eligible and therefore included in the study cohort ([Fig 1](#)).

Study visits

Study visits were conducted at baseline and repeated at 1 and 5 years. Prior to each visit, participants completed a background questionnaire covering demographic details, medical history,



Fig 1. Flow chart for participants invited and recruited into the study, and numbers involved at key time points. CKD, chronic kidney disease; KDIGO, Kidney Disease Improving Global Outcomes.

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smoking history, and medication history. Participants' responses to questions were reviewed at the study visit and clarified as required. At each clinical visit, the participant's height, weight, and waist and hip circumference were measured. Three blood pressure measurements were taken using an oscillometric device (UA-767 Plus 30, A&D Medical) after at least 5 minutes of rest. Readings were repeated until values differed by no more than 10%.

Laboratory methods

Participants collected 3 consecutive days' early morning urine samples and stored these in a refrigerator prior to their study visit for subsequent albumin and creatinine analysis. The mean urine albumin-to-creatinine ratio (uACR) from the 3 specimens was used for analysis. Blood samples were taken at each study visit. Participants were asked to abstain from eating meat for 12 hours prior to the study visit to avoid confounding the serum creatinine assay [19]. Blood and urine samples were analysed in a single clinical laboratory at the Royal Derby Hospital for standard haematological and biochemical variables. Creatinine was measured using a compensated Jaffe method, standardised against an isotope dilution mass spectrometry method, with an inter-assay coefficient of variance of 2.3% at 96 mmol/l (Roche P-analyser, Roche Diagnostics). Cystatin C was measured from serum samples taken at baseline, year 1, and year 5 study visits, stored at -80°C . Measurement was undertaken at the biochemistry laboratory at the John Radcliffe Hospital, Oxford, UK, using a particle-enhanced turbidimetric immunoassay assay (Abbott c16000 Analyser, Abbott Diagnostics) calibrated against the international reference material ERM-DA471/IFCC.63. The assay used has a coefficient of variation of 1.5% at 0.89 mg/l and 1.1% at 4.06 mg/l.

Estimating equations

This analysis compared GFR estimated using the creatinine-based, cystatin-C-based, and combined equations developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), designated $e\text{GFR}_{\text{creat}}$, $e\text{GFR}_{\text{cys}}$, and $e\text{GFR}_{\text{creat-cys}}$, respectively [5,20].

Outcome definitions

We used KDIGO definitions to classify participants' CKD stage according to $e\text{GFR}_{\text{creat}}$, $e\text{GFR}_{\text{cys}}$, and $e\text{GFR}_{\text{creat-cys}}$. The study prespecified endpoint for CKD progression was the development of ESKD or doubling of serum creatinine. However, this endpoint was observed in only 4 participants (0.2%) after 5 years [21], and we therefore used the KDIGO definition of CKD progression, which is a 25% or more loss of GFR coupled with a worsening of eGFR category or a worsening of albuminuria category [6]. Date and cause of death as stated on death certificates was obtained from the Office for National Statistics via the Health and Social Care Information Centre.

Statistical analysis

Analysis was conducted according to a prospective analysis plan (see [S1 Protocol](#) and [S1 Text](#)). Baseline variables were compared according to quartiles of cystatin C, using ANOVA, Kruskal-Wallis, or chi-squared tests as appropriate. Participants were classified according to KDIGO eGFR category initially using $e\text{GFR}_{\text{creat}}$. Reclassification was undertaken using both $e\text{GFR}_{\text{cys}}$ and $e\text{GFR}_{\text{creat-cys}}$. Bland-Altman plots were produced to measure the difference

between $eGFR_{creat}$ and both $eGFR_{cys}$ and $eGFR_{creat-cys}$ across the range of $eGFR$ values. Multivariable linear regression models were constructed using $eGFR_{cys}$ as the dependent variable and $eGFR_{creat}$ as well as clinical variables previously reported as non-GFR determinants of cystatin C as covariates. Non-normally distributed variables (uACR, high-sensitivity C-reactive protein [hsCRP]) were logarithmically transformed prior to multivariable analysis.

We have previously reported multivariable models predicting risk of CKD progression (using the KDIGO definition) and all-cause mortality developed in this cohort [21]. Comparison of these models was undertaken using $eGFR_{cys}$ and $eGFR_{creat-cys}$ in place of $eGFR_{creat}$. Binomial logistic regression models were compared using area under the receiver operating characteristic curve (AUROC) based upon predicted probability of progression.

Cost impact analysis

We used the findings of this study to estimate the cost consequences of implementing cystatin C testing and subsequent monitoring for 12 months as recommended in NICE CKD guidelines for patients with CKD G3aA1 [7]. We assumed that the re-categorising of patients led to the following changes in monitoring by reclassified group: (i) for those classified CKD G3a (no CKD, with diabetes), monitoring continued unchanged, with general practitioner (GP) annual follow-up (eGFR and uACR testing), as recommended by NICE; (ii) for those reclassified as no CKD and without diabetes, the eGFR and uACR tests were dropped from routine monitoring; (iii) for those reclassified as G3b, additional monitoring was added, with eGFR and uACR testing every 6 months via an additional practice nurse consultation; (iv) for those reclassified as G4 or G5, each had a new nephrology outpatient consultation with detailed blood testing and ultrasound, followed by biannual eGFR and uACR testing. The relevant unit costs are shown in Table 1, using costs published by NICE updated to 2015 prices [7].

Results

Baseline data

Cystatin C was measured from stored samples in 1,732 participants at baseline. Baseline values for key variables for this cohort are given in Table 2. Mean \pm standard deviation values for $eGFR_{creat}$, $eGFR_{cys}$, and $eGFR_{creat-cys}$ were 53.6 ± 11.8 , 45.1 ± 16.0 , and 48.3 ± 12.9 ml/min/1.73 m², respectively ($P < 0.001$ for $eGFR_{cys}$ and $eGFR_{creat-cys}$ versus $eGFR_{creat}$). Higher cystatin C was associated with male sex, higher prevalence of previous cardiovascular disease and diabetes mellitus, greater body mass index (BMI), greater waist-to-hip ratio, higher systolic blood pressure, and lower diastolic blood pressure. Haemoglobin, total cholesterol, and serum bicarbonate concentration were lower, and serum uric acid and uACR were higher, in quartiles with higher cystatin C (Table 2).

Table 1. Unit costs.

Unit costs derived from NICE ¹ , updated to 2015	Amount in British pounds
GP annual (simple) consultation for eGFR and uACR	37.50
Practice nurse consultation with phlebotomy	13.23
eGFR and uACR test	6.19
Nephrology first outpatient consultation including ultrasound scan	292.77

¹Chronic kidney disease guideline appendices A–R [22].

eGFR, estimated glomerular filtration rate; GP, general practitioner; NICE, National Institute for Health and Care Excellence; uACR, urine albumin-to-creatinine ratio.

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Table 2. Baseline variables by quartile of baseline cystatin C.

Variable	All participants (n = 1,732)	Participants by cystatin C quartile				P value for trend
		Quartile 1 (n = 444)	Quartile 2 (n = 432)	Quartile 3 (n = 431)	Quartile 4 (n = 425)	
eGFR _{creat} (ml/min/1.73 m ²)	53.6 ± 11.8	63.6 ± 9.7	57.4 ± 7.4	51.1 ± 8.1	41.7 ± 8.9	<0.001
eGFR _{cys} (ml/min/1.73 m ²)	45.1 ± 16.0	65.5 ± 14.4	47.7 ± 3.8	38.6 ± 3.0	27.9 ± 4.9	<0.001
eGFR _{creat-cys} (ml/min/1.73 m ²)	48.3 ± 12.9	64.0 ± 9.2	51.7 ± 4.3	43.7 ± 4.3	33.2 ± 5.7	<0.001
Age (years)	72.9 ± 9.0	68.6 ± 9.0	72.2 ± 8.3	74.4 ± 8.1	76.4 ± 8.8	0.19
Female sex	1,047 (60.4%)	350 (78.8%)	270 (62.5%)	230 (53.4%)	197 (46.4%)	<0.001
Diabetes	292 (16.9%)	43 (9.7%)	60 (13.9%)	92 (21.3%)	97 (22.8%)	<0.001
Current smoker	81 (4.7%)	17 (3.8%)	18 (4.2%)	18 (4.2%)	28 (6.6%)	0.20
Previous CVD	385 (22.2%)	67 (15.1%)	84 (19.4%)	111 (25.8%)	123 (28.9%)	<0.001
Thyroid disorder	217 (12.5%)	61 (13.7%)	58 (13.4%)	44 (10.2%)	54 (12.7%)	0.39
Haemoglobin (g/l)	132 ± 14	135 ± 13	134 ± 13	133 ± 14	128 ± 16	<0.001
Corrected calcium (mmol/l)	2.38 ± 0.10	2.38 ± 0.10	2.38 ± 0.09	2.38 ± 0.10	2.37 ± 0.10	0.37
Phosphate (mmol/l)	1.11 ± 0.18	1.11 ± 0.18	1.10 ± 0.19	1.09 ± 0.16	1.12 ± 0.18	0.07
Albumin (g/l)	40.7 ± 3.2	41.3 ± 3.0	41.0 ± 3.0	40.4 ± 3.1	40.0 ± 3.5	0.28
Bicarbonate (mmol/l)	25.5 ± 2.7	26.1 ± 2.4	25.7 ± 2.5	25.4 ± 2.7	24.9 ± 3.0	<0.001
Total cholesterol (mmol/l)	4.8 ± 1.2	5.1 ± 1.1	4.8 ± 1.1	4.7 ± 1.2	4.5 ± 1.2	0.04
Uric acid (μmol/l)	384 ± 91	334 ± 75	364 ± 76	398 ± 78	443 ± 96	<0.001
BMI (kg/m ²)	29.0 ± 5.1	28.4 ± 4.9	28.7 ± 4.7	29.3 ± 4.8	29.7 ± 5.9	0.003
Waist-to-hip ratio	0.91 ± 0.09	0.87 ± 0.08	0.90 ± 0.09	0.92 ± 0.08	0.94 ± 0.09	0.001
SBP (mm Hg)	134 ± 18	133 ± 18	134 ± 17	135 ± 18	134 ± 21	0.001
DBP (mm Hg)	73 ± 11	76 ± 11	73 ± 10	73 ± 11	70 ± 11	0.008
uACR (mg/mmol)	0.33 (0.00–1.50)	0.13 (0.00–0.58)	0.16 (0.00–0.97)	0.50 (0.00–2.07)	1.17 (0.15–4.20)	<0.001
hsCRP (mg/l)	2.2 (1.1–4.6)	1.7 (0.8–3.4)	2.0 (1.1–3.6)	2.5 (1.3–5.5)	3.3 (1.7–6.2)	<0.001

Data shown are mean ± standard deviation, number (percent), or median (lower quartile–upper quartile).

BMI, body mass index; creat, creatinine; cys, cystatin C; creat-cys, creatinine and cystatin C; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure; uACR, urine albumin-to-creatinine ratio.

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A comparison of the frequency of people in each eGFR category using the different equations is shown in Fig 2. Fewer participants had a baseline eGFR ≥ 60 ml/min/1.73 m² using either eGFR_{cys} or eGFR_{creat-cys} compared to eGFR_{creat}. Similarly, both eGFR_{cys} and eGFR_{creat-cys} classified more participants as having CKD G3b/G4 disease compared to eGFR_{creat}.

The use of eGFR_{cys} in the 653 people with eGFR_{creat} CKD G3aA1 at baseline reclassified 50 (7.7%) to eGFR ≥ 60 ml/min/1.73 m² (i.e., no CKD), 356 (54.5%) to G3b, and 29 (4.5%) to G4 or G5. Similarly, using eGFR_{creat-cys} reclassified 36 (5.5%) to no CKD, 239 (36.6%) to G3b, and 2 (0.3%) to G4 or G5 (Table 3). Application of eGFR_{cys} to the whole study population reclassified 57 of 784 (7.3%) with eGFR_{creat} CKD G3a to eGFR ≥ 60 ml/min/1.73 m² and 488 (62.2%) to CKD G3b or worse (Table 4). Similarly, in the whole study population, eGFR_{creat-cys} reclassified 4.7% of participants (37 of 784) with eGFR_{creat} CKD G3a to eGFR ≥ 60 ml/min/1.73 m² and 311 (39.7%) to CKD G3b or G4 (Table 5).

Bland–Altman plots

Bland–Altman plots in the whole cohort showed that for the majority of participants, eGFR_{creat} was greater than eGFR_{cys} and eGFR_{creat-cys} (Fig 3). Mean difference was +8.4 ml/min/1.73 m²

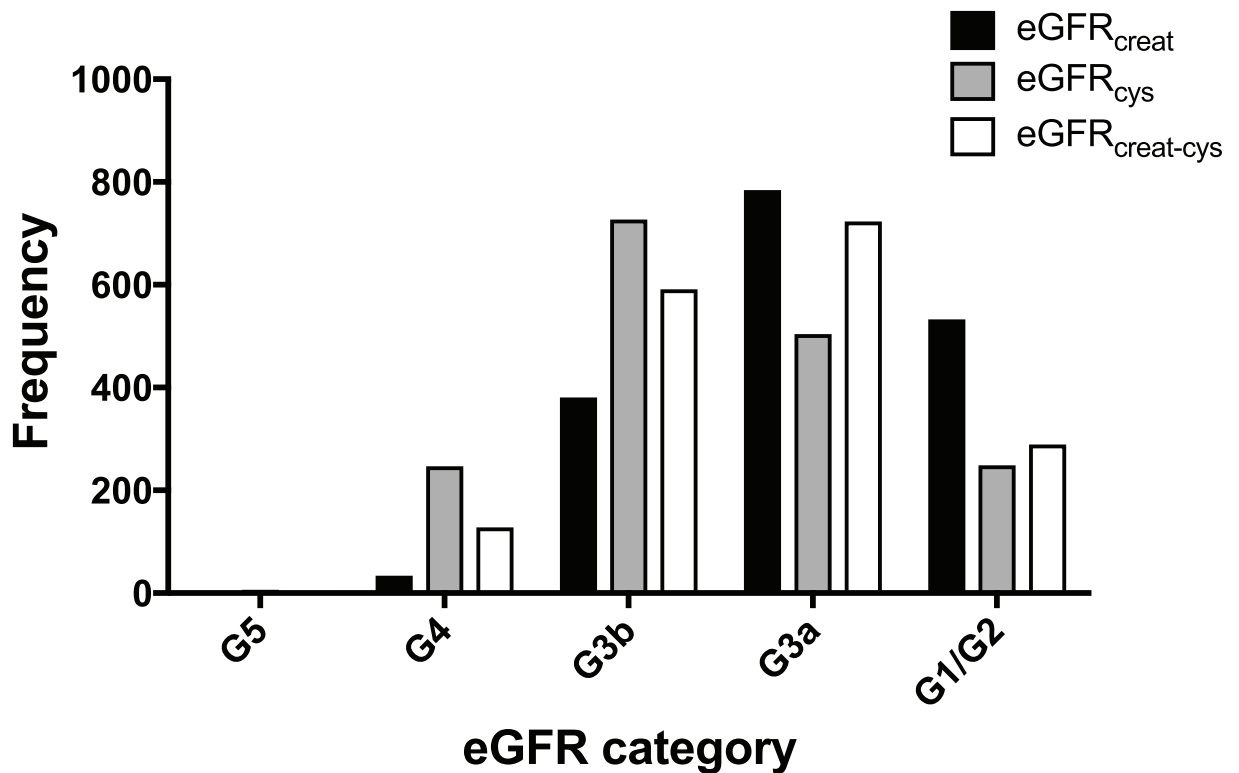


Fig 2. Histogram showing frequency of people in each eGFR category at baseline using different estimating equations. creat, creatinine; cys, cystatin C; creat-cys, creatinine and cystatin C; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate.

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between eGFR_{creat} and eGFR_{cys} and +5.3 ml/min/1.73 m² between eGFR_{creat} and eGFR_{creat-cys}. Both plots showed a small minority of cases, at higher mean eGFR, for which eGFR_{cys} or eGFR_{creat-cys} was greater than eGFR_{creat}.

Non-GFR determinants of eGFR_{cys}

Non-GFR determinants of eGFR_{cys} at baseline were assessed using linear regression, with correction for baseline eGFR_{creat}. In fully adjusted models, a range of factors remained significant including age, smoking status, and BMI. Other significant determinants included markers of inflammation and non-traditional cardiovascular risk factors (haemoglobin, uric acid, albumin, uACR, and hsCRP) (S1 Table).

Table 3. Reclassification in 653 participants classified as CKD G3aA1 by eGFR_{creat} at baseline using eGFR_{cys} and eGFR_{creat-cys}.

Estimating equation	eGFR ≥ 60 ml/min/1.73 m ²	CKD G3a	CKD G3b	CKD 4	CKD 5
eGFR _{cys}	50 (7.7%)	218 (33.4%)	356 (54.5%)	28 (4.3%)	1 (0.2%)
eGFR _{creat-cys}	36 (5.5%)	376 (57.6%)	239 (36.6%)	2 (6.3%)	0

Data shown are number (percent).

CKD, chronic kidney disease; creat, creatinine; cys, cystatin C; creat-cys, creatinine and cystatin C; eGFR, estimated glomerular filtration rate.

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Table 4. Baseline eGFR_{creat} category and reclassification using eGFR_{cys} in all study participants.

Baseline eGFR _{creat} category	eGFR _{cys} category					Total
	G1/G2	G3a	G3b	G4	G5	
G1/G2	182 (34.1%)	251 (47.1%)	96 (18.0%)	4 (0.8%)	0	533 (30.8%)
G3a	57 (7.3%)	239 (30.5%)	446 (56.9%)	41 (5.2%)	1 (0.1%)	784 (45.2%)
G3b	10 (2.6%)	12 (3.1%)	183 (48.0%)	174 (45.7%)	2 (0.5%)	381 (22.0%)
G4	0	2 (5.9%)	2 (5.9%)	28 (82.4%)	2 (5.9%)	34 (2.0%)

Data shown are number (percent). Cohen's Kappa for agreement between eGFR_{creat} and eGFR_{creat-cys} = 0.13. creat, creatinine; cys, cystatin C; eGFR, estimated glomerular filtration rate.

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Change in eGFR over 5 years

Nine hundred ninety-nine participants had cystatin C measured at both baseline and year 5 (Fig 1). There was a weak correlation between 5-year change in eGFR_{cys} and 5-year change in eGFR_{creat} (Pearson's correlation coefficient, $r = 0.33$, $P < 0.001$), and a moderate correlation between 5-year change in eGFR_{creat-cys} and 5-year change in eGFR_{creat} ($r = 0.76$, $P < 0.001$).

Over 5 years, the KDIGO definition for CKD progression based on 25% loss of eGFR and a worsening of eGFR category or albuminuria category was met in 105 of 999 participants (10.5%) using eGFR_{creat}, 182 (18.2%) using eGFR_{cys}, and 135 (13.5%) using eGFR_{creat-cys}.

Risk prediction

Overall, 306 participants (17.7%) met the KDIGO criteria for CKD progression at 5 years, and 247 (14.2%) died. Replacing baseline eGFR_{creat} with eGFR_{cys} or eGFR_{creat-cys} in previously developed multivariable prediction models for CKD progression [21] did not improve discrimination. The AUROC was comparable for all 3 models (Table 6). Similarly, in multivariable Cox proportional hazards models for all-cause mortality over 5 years, similar hazard ratios were obtained for eGFR with each estimating equation (Table 6).

Cost impact

The impacts on National Health Service (NHS) costs for groups reclassified with CKD G3aA1 by eGFR_{cys} or eGFR_{creat-cys} are summarised in Table 7, based on conservative assumptions. The direct cost of adding eGFR_{cys} testing to existing tests would be fairly low based on NICE's estimated cost of just over £3 per test. However, the total cost impact of providing recommended monitoring and referral would be much greater, at £20 per person (£12,843 for the 653 persons in this study). Thus, the combined total cost impact would be an increase of £23 (£20 + £3) per person. This impact would be less if using the combined eGFR_{creat-cys} equation,

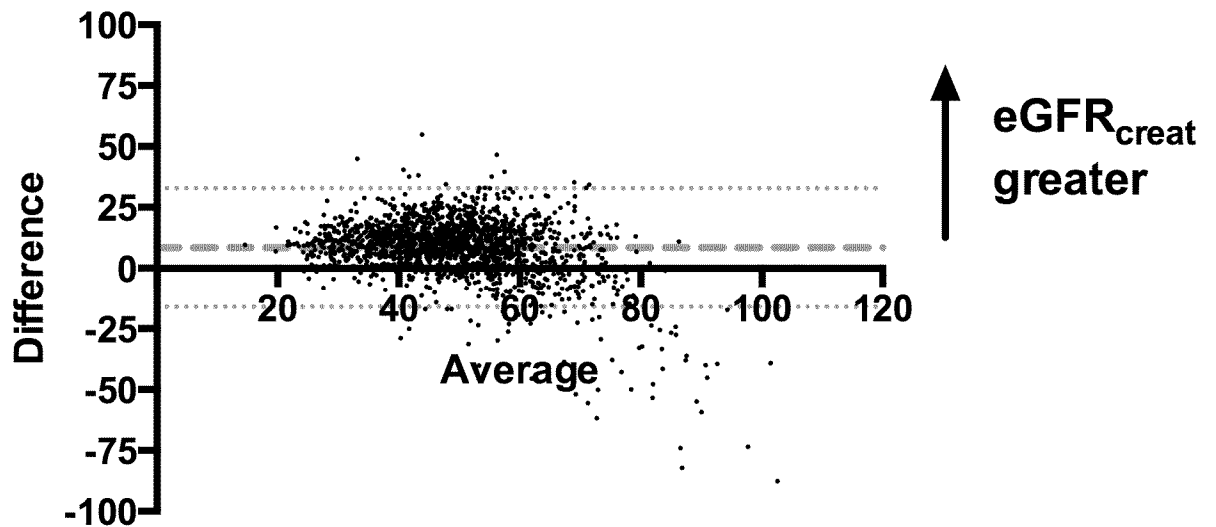
Table 5. Baseline eGFR_{creat} category and reclassification using eGFR_{creat-cys} in all study participants.

Baseline eGFR _{creat} category	eGFR _{creat-cys} category					Total
	G1/G2	G3a	G3b	G4	G5	
G1/G2	249 (46.7%)	274 (51.4%)	10 (1.9%)	0	0	533 (30.8%)
G3a	37 (4.7%)	436 (55.6%)	309 (39.4%)	2 (0.3%)	0	784 (45.2%)
G3b	3 (0.8%)	13 (3.4%)	270 (70.9%)	95 (24.9%)	0	381 (22.0%)
G4	0	0	2 (5.9%)	31 (91.2%)	1 (2.9%)	34 (2.0%)

Data shown are number (percent). Cohen's Kappa for agreement between eGFR_{creat} and eGFR_{creat-cys} = 0.37. creat, creatinine; creat-cys, creatinine and cystatin C; eGFR, estimated glomerular filtration rate.

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A: Bland-Altman plot of baseline $eGFR_{creat}$ and $eGFR_{cys}$



B: Bland-Altman plot of baseline $eGFR_{creat}$ and $eGFR_{creat-cys}$

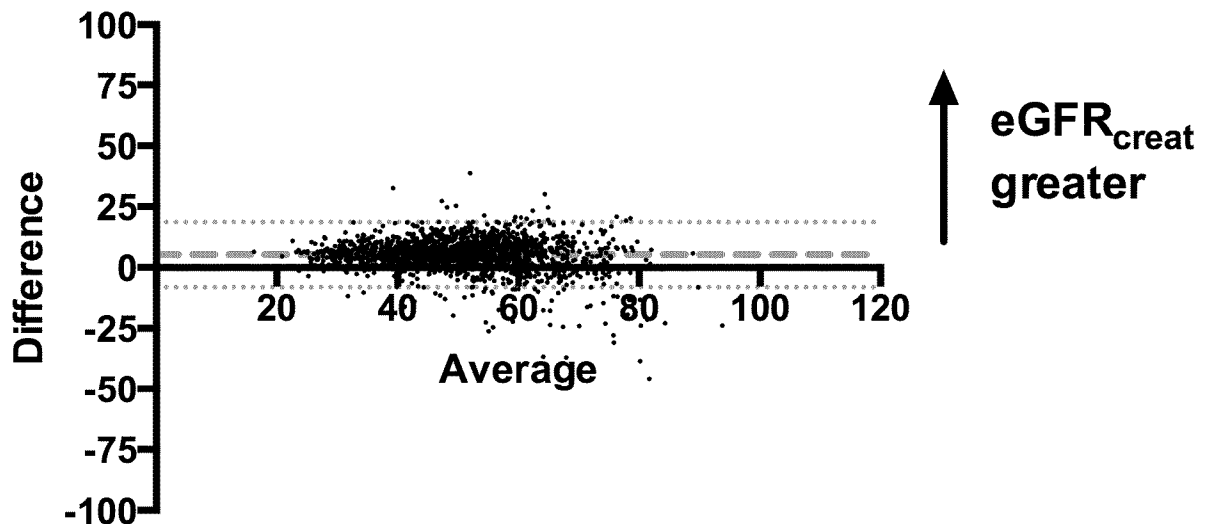


Fig 3. Bland-Altman plots comparing $eGFR_{creat}$ to $eGFR_{cys}$ and $eGFR_{creat-cys}$. (A) $eGFR_{creat}$ versus $eGFR_{cys}$; (B) $eGFR_{creat}$ versus $eGFR_{creat-cys}$. Dashed lines show mean difference between the 2 estimates of glomerular filtration rate. Dotted lines show 95% CI for mean difference between the 2 estimates. creat, creatinine; creat-cys, creatinine and cystatin C; cys, cystatin C; eGFR, estimated glomerular filtration rate.

<https://doi.org/10.1371/journal.pmed.1002400.g003>

with a total cost of £8 per person. This lower cost results from fewer people being reclassified in either direction (Table 7).

Table 6. Risk prediction models for CKD progression in 999 participants and all-cause mortality in 1,732 participants using different estimating equations for eGFR.

Risk prediction	Estimating equation	Odds ratio or hazard ratio (95% CI)	P value	AUROC
Models for KDIGO CKD progression	eGFR _{creat}	0.984 (0.971–0.998)	0.023	0.722
	eGFR _{cys}	0.982 (0.971–0.993)	0.001	0.726
	eGFR _{creat-cys}	0.978 (0.965–0.991)	0.001	0.726
Models for all-cause mortality	eGFR _{creat}	0.973 (0.960–0.986)	<0.001	
	eGFR _{cys}	0.975 (0.963–0.987)	<0.001	
	eGFR _{creat-cys}	0.967 (0.954–0.981)	<0.001	

All progression models are adjusted for age, sex, urine albumin-to-creatinine ratio, haemoglobin, bicarbonate, and diabetes. All odds ratios given per ml/min/1.73 m². All survival models are adjusted for age, sex, urine albumin-to-creatinine ratio, haemoglobin, albumin, bicarbonate, diabetes, and previous cardiovascular disease. All hazard ratios are given per ml/min/1.73 m².

AUROC, area under the receiver operating characteristic curve; CKD, chronic kidney disease; creat, creatinine; cys, cystatin C; creat-cys, creatinine and cystatin C; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes.

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Discussion

Our results indicate that for the majority with CKD stage 3 (confirmed by 2 eGFR_{creat} values) in primary care, use of eGFR_{cys} or eGFR_{creat-cys} results in lower estimates of GFR than eGFR_{creat}. The use of eGFR_{cys} as recommended by NICE to confirm an eGFR_{creat}-based diagnosis of CKD G3aA1 resulted in reclassification of 7.7% as not having CKD, but a far greater proportion (59.0%) were reclassified as having more advanced CKD (G3b–G5). Thus, in a

Table 7. Cost impact of cystatin C testing in the year of introduction, by GFR estimating equation, at 2015 prices (British pounds).

Outcome	Reclassification status	Reference ¹	Change in cost	Unit cost (£)	Using eGFR _{cys}		Using eGFR _{creat-cys}	
					Number affected	Total cost (£)	Number affected	Total cost (£)
Change in management								
Stop monitoring	G1/G2, no DM, no HT	NICE CKD 182	Decrease	7.50	15	-563	11	-413
Diabetes schedule unchanged	G1/G2, DM	NICE DM 28	Nil		6	0	0	0
Exclude eGFR and uACR test from annual review	G1/G2, HT	NICE HT 127	Decrease	6.19	29	-180	22	-136
Unchanged from annual GP assessment of eGFR and uACR	G3a		Nil		218	0	376	0
Biannual assessment of eGFR and uACR ²	G3b	NICE CKD 182	Increase	13.23	356	4,711	239	3,163
Nephrology, followed by biannual GP assessment of eGFR and uACR ³	G4, G5	NICE CKD 182	Increase	306.00	29	8,874	2	612
Total increase						12,843		3,226
Increase £/patient (monitoring)						20		5
Total increase £/patient						23		8

¹References are NICE guidance documents. Numbers in the column are guideline numbers (see <https://www.nice.org.uk/guidance>).

²Unit cost for biannual assessment assumes this involves 1 additional visit to a practice nurse with phlebotomy for eGFR and uACR testing.

³Unit cost for nephrology followed by biannual GP visit assumes this involves 1 extra outpatient consultation plus 1 additional visit to a practice nurse with phlebotomy for eGFR and uACR testing.

CKD, chronic kidney disease; creat-cys, creatinine and cystatin C; cys, cystatin C; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; GP, general practitioner; HT, hypertension; NICE, National Institute for Health and Care Excellence; uACR, urine albumin-to-creatinine ratio.

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primary care setting, the potential benefit of reducing over-diagnosis of CKD with $eGFR_{cys}$ would be eliminated by the unintended consequence of greater reclassification to more advanced CKD requiring more frequent monitoring and increased referrals to secondary care. Additionally, the use of $eGFR_{cys}$ did not improve discrimination in risk prediction models in a primary care population. Overall estimated costs would be increased by £23 per patient with $eGFR_{cys}$ and £8 per patient with $eGFR_{creat-cys}$.

Our results differ in many respects from those of a large meta-analysis that evaluated the clinical impact of using cystatin C versus creatinine to estimate GFR in 11 general population cohorts and 5 CKD cohorts [23]. In the meta-analysis, though no difference was observed in mean $eGFR$ calculated by the different methods, use of $eGFR_{cys}$ resulted in a higher prevalence of $eGFR < 60$ ml/min/1.73 m² than either $eGFR_{creat}$ or $eGFR_{creat-cys}$ (13.7%, 9.7%, and 10.0%, respectively). On the other hand, use of $eGFR_{cys}$ resulted in reclassification of 35%–47% of participants with CKD G3a to $GFR \geq 60$ ml/min/1.73 m², whereas a lower proportion (21%–27%) were reclassified to CKD G3b or worse. Moreover, reclassification to a less severe category was associated with lower risks of all-cause mortality, cardiovascular mortality, and ESKD [23]. One reason for the differences between these observations and ours is important differences in the cohorts studied. The mean age of 60 and 55 years for the general population and CKD cohorts, respectively, was substantially lower than the mean age of our cohort (73 years). This is an important distinction because our cohort is more representative of the majority of people affected by CKD in developed countries with predominantly white populations. A second important difference is that the studies included in the meta-analysis relied on only 1 abnormal $eGFR_{creat}$ for the diagnosis of CKD, whereas we required confirmation with 2 abnormal $eGFR_{creat}$ values at least 90 days apart for study eligibility. In our study, those classified as CKD G3a at baseline therefore had a minimum of 3 abnormal $eGFR_{creat}$ values. It is likely that simply retesting $eGFR_{creat}$ would have reclassified a proportion of those included in the meta-analysis as not having CKD, and this would reduce the impact of reclassification by $eGFR_{cys}$. In a population-based study in England, use of $eGFR_{cys}$ resulted in a higher prevalence of CKD G3–G5 than $eGFR_{creat}$ (7.7% versus 5.2%, respectively) [17]. In this study, similar to the above meta-analysis, 37% of those with CKD G3aA1 defined by $eGFR_{creat}$ were reclassified by $eGFR_{cys}$ as not having CKD, but the proportion reclassified to an $eGFR$ category indicating more severe CKD was not reported. Like the meta-analysis, the participants in this study were much younger than our cohort (median age 50 years), and only a single creatinine measurement was used to define CKD. In addition, the cystatin C assay used was not standardised to international reference material, and the CKD-EPI equation could not be used [17]. In contrast, an analysis of National Health and Nutrition Examination Survey data revealed higher prevalence of reduced GFR by $eGFR_{cys}$ than $eGFR_{creat}$ in both diabetic and non-diabetic participants [24].

In our study, $eGFR_{cys}$ identified a higher proportion of participants as having progressive CKD (18.2%) than $eGFR_{creat}$ (10.5%) or $eGFR_{creat-cys}$ (13.5%). Thus, in addition to the impact of the lower baseline $eGFR$ values seen with $eGFR_{cys}$, higher apparent progression rates would further promote the referral of patients from primary to secondary care. One could argue that increased referral would be appropriate if patients were at increased risk, but the very low rate of progression to ESKD observed in our study population after 5 years (0.2%) [21] implies that use of $eGFR_{cys}$ in this primary care population would tend to increase referrals and frequency of testing of people with low-risk disease who would be unlikely to benefit.

There is ongoing debate concerning the appropriateness of diagnosing CKD in older people with category G3a $eGFR$ and no proteinuria [25]. In this analysis, we applied current guidelines to diagnosis of CKD in our cohort. We have previously described the low rates of CKD progression and relatively high rates of ‘remission’ in this population [21]. Additionally, recent

results from the Berlin Initiative Study (BIS) have shown that eGFR in older adults strongly depends upon the estimating equation used [26]. The BIS equations (creatinine only and combined creatinine and cystatin C) were developed in a cohort of people over the age of 70 years. These equations tend to produce lower eGFR values than the corresponding CKD-EPI equations and are more accurate in predicting measured GFR [27]. Comparable results have been shown using the full age spectrum (FAS) equation [28]. Our study focussed on the CKD-EPI equations as these have been incorporated into KDIGO and NICE guidance and are in widespread use clinically.

Several studies have reported that, like all endogenous markers of GFR, serum cystatin C concentration is independently associated with several non-GFR determinants including age, sex, diabetes, markers of obesity, inflammation, and smoking [10–13]. Though we did not have measured GFR data, multivariable analysis corrected for eGFR_{creat} confirmed independent associations of eGFR_{cys} with age, serum albumin, serum uric acid, haemoglobin, BMI, uACR, hsCRP, and current smoking (S1 Table) [29]. These observations are important because several of these non-GFR determinants are also risk factors for cardiovascular disease, and this may in part explain the better performance of eGFR_{cys} as a risk factor for adverse outcomes in CKD cohorts and populations without CKD. Indeed, some have suggested that the ability of cystatin C concentration to predict mortality may have little to do with its association with GFR but instead is largely attributable to the non-GFR determinants of cystatin C [30,31]. Alternatively, other investigators have proposed that in states of inflammation, filtration of cystatin C at the glomerulus is impaired, producing underestimates of GFR [32]. In addition, understanding the non-GFR determinants of cystatin C is important for identifying patient groups in whom eGFR_{cys} will be unreliable. Our data, though limited by lack of measured GFR, confirm previous reports suggesting that eGFR_{cys} is likely to be less accurate for estimating GFR in elderly and obese patients as well as those with albuminuria or evidence of inflammation and in current smokers. However, there may be situations where measurement of eGFR_{cys} may be preferred to eGFR_{creat}, for example in the assessment of renal function in younger people with extremes of body habitus and muscle mass.

Reduced GFR is widely recognised as an independent risk factor for multiple adverse outcomes including acute kidney injury, ESKD, cardiovascular mortality, and all-cause mortality [33–35]. Several papers have reported improved discrimination if eGFR_{cys} is used in risk prediction analyses instead of eGFR_{creat}, though it is unclear whether this is due to improved GFR estimation or associations with the non-GFR determinants of cystatin C. In our cohort, eGFR_{cys} did not improve discrimination in risk prediction analyses for CKD progression or all-cause mortality, suggesting that widespread use in primary care will not improve risk prediction [15,16].

Our assessment of the cost associated with implementing NICE guidance to use eGFR_{cys} to confirm a diagnosis in those classified as CKD G3aA1 by eGFR_{creat} resulted in an overall increase in cost of £23 per patient because the cost savings resulting from reduced numbers diagnosed with CKD were far outweighed by the increased costs associated with a requirement for increased monitoring and referral in the large proportion reclassified to a more advanced stage of CKD. The total number of patients meeting the inclusion criteria of this study in the adult population of England can be estimated approximately from the Health Survey for England as 1.36 million (prevalence in adults of G3aA1 of 3.2%) [9]. If the increase of £23 per patient due to implementation of the NICE guidance was applied to each of these patients, the total additional cost to the NHS would be approximately £31 million per year. A lower total national cost of about £11 million would apply if instead the combined eGFR_{creat-cys} equation was used. This cost could potentially be justified if the use of eGFR_{cys} were associated with higher-risk patients being successfully treated with more intensive treatment or referral, but we were unable to demonstrate improved risk prediction in this predominantly low-risk study

population. In interpreting these national cost extrapolations, it should be remembered that, like most epidemiological studies, the Health Survey for England measured only a single eGFR value and may therefore have overestimated the true prevalence of CKD G3aA1.

Study strengths and limitations

Important strengths of this study are individual recruitment and clinical assessment at baseline, prospective protocol-driven follow-up, and a requirement for 2 eGFR readings of <60 ml/min/1.73 m² prior to inclusion in the study cohort [36,37]. This last strength is of particular significance because the majority of published studies have adopted the epidemiological study approach of requiring only 1 abnormal eGFR for CKD diagnosis. Moreover, our study population was predominantly elderly, and most participants had only mildly reduced GFR. This is typical of the majority affected by CKD in developed countries [8] and is representative of populations in which NICE and KDIGO anticipated that use of eGFR_{cys} would reduce over-diagnosis of CKD. We were also able to evaluate the short-term cost implication of using the different equations.

We must, however, concede several important limitations of the study. We were limited by the lack of a measured GFR at baseline in order to compare estimating equations to a 'gold standard'. However, the aim of this study was to assess primarily the clinical impact of introducing eGFR_{cys} in primary care, where few people have a measured GFR, rather than the accuracy of the estimating equations. Few people with CKD have a measured GFR, and our study therefore reflects the situation in clinical practice. The lack of a measured GFR also impacts upon our assessment of non-GFR determinants of eGFR_{cys} due to potential confounding by non-GFR determinants of eGFR_{creat} (used as a correction in the analysis instead of measured GFR). Nevertheless, our results are consistent with previous published studies and strengthen the evidence by showing that non-GFR determinants of cystatin C are an important consideration in the primary care setting. The risk prediction models described in this paper were used to show that the use of eGFR_{cys} did not improve discrimination compared to eGFR_{creat} in this cohort. It was not our intention to develop risk prediction models for general application, and we concede that external validation would be required before this could be recommended. Our study population was predominantly white and elderly (mean age 73 years), and most had only mild reductions in GFR (mean eGFR_{creat} 53.6 ml/min/1.73 m²). As discussed above, this is in some respects a strength, but we concede that our results may not be applicable to younger or more ethnically diverse populations or to those in secondary care with more advanced CKD. The number of events of death and CKD progression was also relatively low, and we may therefore have lacked statistical power to detect minor improvement in risk prediction with eGFR_{cys}. Our cost impact analysis was limited to the year of introduction of cystatin C testing. Lifetime (or long term) costing would require more complex modelling that is beyond the scope of this paper.

Conclusions

We have found that in an elderly population in primary care, application of NICE and KDIGO recommendations to use eGFR_{cys} to confirm a diagnosis of CKD in those classified as CKD G3aA1 by eGFR_{creat} results in a greater proportion of individuals being reclassified to an eGFR category indicating more severe CKD than reclassified to an eGFR category indicating no CKD. Additionally, eGFR_{cys} cannot be recommended to improve risk prediction in this population because it did not improve discrimination in risk prediction models for adverse outcomes compared to eGFR_{creat}. Our data therefore do not support implementation of these recommendations in primary care. Nevertheless, it is likely that eGFR_{cys} will be helpful in

obtaining a more accurate estimate of GFR in people at extremes of muscle mass, in whom $eGFR_{creat}$ is known to be inaccurate, but account should also be taken of the non-GFR determinants of cystatin C. Further studies are warranted to define the most appropriate clinical application of $eGFR_{cys}$ and $eGFR_{creat-cys}$.

Supporting information

S1 STARD Checklist. STARD statement for reporting of diagnostic accuracy studies.
(DOCX)

S1 STROBE Checklist. STROBE statement for reporting of cohort studies.
(DOCX)

S1 Table. Univariate and multivariable non-GFR determinants of $eGFR_{cys}$.
(DOCX)

S1 Protocol. Current study protocol.
(DOC)

S1 Text. Application submitted for funding from the Dunhill medical trust.
(DOC)

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