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Requirement for cystatin C testing in chronic kidney disease:

a retrospective population-based study

Abstract

Background
Creatinine-based estimated glomerular filtration rate (eGFR) determines chronic kidney disease (CKD) stage, but underestimates renal function. The 2014 updated guidance from the National Institute for Health and Care Excellence (NICE) recommends that GPs reduce overdiagnosis of CKD stage 3a (eGFR 45–60 ml/min/1.73 m^2) by using the renal biomarker cystatin C.

Aim
To determine the population requirement for cystatin C testing, compared with current national availability of the assay.

Design and setting
Retrospective study of primary care laboratory requests in Oxfordshire, England.

Method
The first creatinine results from tests ordered in primary care over a 6-year period (2008–2014) in a population of 600 000 in Oxfordshire were analysed and the number of patients with CKD stage 3a without proteinuria (who, in accordance with NICE guidance, required cystatin C) was determined. A conservative estimate of the national need was provided by scaling the population of Oxfordshire to the national population (CKD prevalence in the county is below the national average). Cystatin C assay availability was determined using national databases of laboratory assay provision.

Results
From a population of 600 000, there were 22 240 individuals with stable stage 3a CKD and no proteinuria. As the population of Oxfordshire equates to 1% of the UK population, there is an initial requirement for at least 2 million people to have their CKD status determined with cystatin C testing. Eight laboratories (2.1% of UK laboratories) reported cystatin C assay provision.

Conclusion
There is a substantial gap between cystatin C assay requirements in primary care and national assay provision. This is a major barrier to implementing NICE guidance.

Keywords
chronic kidney disease; cystatin C; diagnosis; general practice; kidney diseases; laboratory provision; NICE guidance.

INTRODUCTION

Chronic kidney disease (CKD) increases mortality and healthcare resource usage,[1] and the majority of patients who have it are diagnosed and managed in general practice. CKD is staged according to estimated glomerular filtration rate (eGFR) and level of proteinuria.[2] eGFR is routinely calculated from serum creatinine, which is cheap to analyse and universally available; however, at higher levels of measured GFR, the eGFR formulae have a tendency to underestimate true renal function.[3] This results in the overdiagnosis of CKD, thereby increasing healthcare costs as well as resulting in an unnecessary burden for patients.

Cystatin C is an alternative biomarker of renal function; due to muscle mass, it displays less variation than creatinine and offers greater accuracy of GFR estimation, which improves the relationship between eGFR and subsequent risk of CKD-related outcomes, such as cardiovascular death and end-stage renal failure.[4]

In the UK, the National Institute for Health and Care Excellence (NICE) has published revised guidance for the diagnosis and monitoring of CKD.[5] Recognising that the newly recommended Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for estimating eGFR from creatinine still has bias at higher levels of eGFR,[3] NICE recommends testing with cystatin C for patients whose eGFR calculated from serum creatinine is in the stage 3a range (45–59 ml/min/1.73 m^2). Although there are many formulae that can transform cystatin C into eGFR,[6–10] the NICE guidance recommends the CKD-EPIcys equation, which combines creatinine and cystatin C.[5] Compared with the standard creatinine-based CKD-EPI equation, using the CKD-EPIcys equation to determine eGFR in large prospective cohort studies improves the classification of risk.[4]

Irrespective of the choice of equation to transform cystatin C, there is likely to be a substantial need for UK laboratories to offer cystatin C testing to general practice at substantial scale and pace if NICE guidance is to be implemented within a reasonable time frame. The authors set out to determine the likely population need for cystatin C testing, and to compare this with the current scale of provision using two indicators of laboratory availability of the assay.

METHOD

The proportion of primary care patients in a population of 600 000 in Oxfordshire[11] who would require testing with cystatin C as part of CKD diagnosis and monitoring in accordance with NICE guidance was determined. The first creatinine results from tests ordered in primary care over a 6-year period (2008–2014) were analysed to assess the scale of the need for cystatin C

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How this fits in

A cystatin C-based estimated glomerular filtration rate improves the accuracy of chronic kidney disease staging and is recommended by the National Institute for Health and Care Excellence (NICE). However, only a tiny proportion of UK laboratories can test for cystatin C. This study determines the large scale of cystatin C testing that will be needed for accurate diagnosis in primary care and makes it clear that, unless commissioners address this assay provision gap, NICE guidance cannot be implemented. This would leave patients at risk of overdiagnosis, unnecessary prescribing, and unnecessary laboratory monitoring.

testing and the stability of this requirement over time.

The clinical biochemistry laboratory at the John Radcliffe Hospital in Oxford, England, used a modified Jaffe analytical technique with materials traceable to isotope dilution mass spectrometry methods, so creatinine assay results were standardised throughout the time period of analysis. The eGFR from creatinine was calculated using the CKD-EPI equation and the number of patients with stable stage 3a CKD — patients with a minimum of two eGFR results in the 3a range (45–60 ml/min/1.73 m^2) at least 3 months apart — was ascertained. For patients with a first eGFR result in the 3a range in the last sampled year (2014), follow-up tests in the 12 months after the end of the sampling window were sought in order to determine whether they had stable 3a CKD. Patients with an albumin:creatinine ratio (ACR) of >3 mg/mmol were excluded as they were deemed to have CKD and did not need additional testing with cystatin C.[5] As a result, the 'catch-up testing' required in the population to meet NICE guidance would feature the remaining patients with stable stage 3a CKD without proteinuria.

Two indicators of cystatin C assay availability were obtained. UK laboratories are required to participate in proficiency testing to achieve accreditation. The UK National External Quality Assessment Service (UK NEQAS) represents a network of proficiency testing schemes, one of which offers clinical laboratories a service to assess the performance of GFR markers, including creatinine and cystatin C. The authors ascertained, from the scheme provider, the number of laboratories participating in the UK NEQAS quality assessment scheme for both cystatin C and creatinine at two time points 1 year apart to assess for growth in capacity. The second approach was to search for cystatin C on the website AssayFinder (www.assayfinder.com), a widely used web resource that enables providers of specific laboratory tests to be identified.

RESULTS

From 2008 until 2014, a total of 29 987 individuals from the study cohort had evidence of stable stage 3a CKD. Of these, 7747 patients had an ACR of >3 mg/mmol, leaving 22 240 patients without evidence of proteinuria. In addition, a further 3875 patients had one eGFR in the stage 3a range but no further blood tests within the 6-year sampling frame.

Table 1 shows the numbers of patients with stable 3a CKD in each year of the study and the number with an ACR of >3 mg/mmol. The number of new individuals requiring cystatin C testing falls each year as population coverage of prevalent cases increases with time from different blood-testing practices in the community. As the population of Oxfordshire equates to 1% of the UK population,[11] and assuming that the level of primary care blood testing is similar in other areas of the UK, there is an initial requirement for at least 2 million people to have their CKD status determined with cystatin C testing.

As of April 2015, compared with 340 laboratories that reported creatinine on the UK NEQAS scheme for GFR estimations, only four (just 1.2% of participating laboratories) reported cystatin C. In June 2016, the comparative enrolment was eight reporting cystatin C and 378 reporting creatinine (2.1% of participants). In April 2015, the AssayFinder website documented three UK laboratories offering cystatin C analysis; this figure was unchanged by July 2016.

Table 1. Individuals with stable CKD stage 3a by year of first test, sub-group with proteinuria, and cumulative total (2008–2014)

Year	Evidence of stable CKD 3a, *n*	ACR >3 mg/mmol, *n*	Cumulative total with stable 3a CKD who would require cystatin C testing
2008	20 129	5094	15 035
2009	4195	1159	18 071
2010	2208	624	19 655
2011	1146	317	20 484
2012	988	219	21 253
2013	735	202	21 786
2014	586	132	22 240

ACR = albumin:creatinine ratio. CKD = chronic kidney disease.

DISCUSSION

Summary

A substantial number of patients will require additional testing with cystatin C if the latest NICE CKD guidance is to be implemented. Although a reduction in the proportion of all eGFR results from primary care that are in the CKD 3a range was observed over a 5-year period, there were still large numbers of patients whose CKD status cannot be fully determined with creatinine-based measures alone.

The findings from two independent estimates of routine cystatin C availability suggest that only a few laboratories have this assay available with an accredited testing process. There was also very little increase in availability in the 12 months until July 2016. This implies that there is a very large gap between the need for the cystatin C assay, in order to be able to implement NICE guidance, and its provision in routine UK health care.

Strengths and limitations

It is possible that some UK laboratories are enrolled with a quality control scheme provider other than UK NEQAS. The clinical biochemistry laboratory in Oxford participates in an additional Europe-wide proficiency testing organisation, the Swedish EQUALIS scheme, but this has only 51 laboratories registered in Europe providing cystatin C testing. This would suggest that cystatin C availability is very limited in other European countries.

Cystatin C can be undertaken on a wide range of commonly available instruments,[6] suggesting that routine availability is not hindered by a lack of testing resources within NHS laboratories. Furthermore, although the estimate of the UK-wide requirement for cystatin C testing rests on a number of assumptions, including the level of primary care blood testing being similar in the rest of the UK, the authors believe it is conservative as the prevalence of CKD in Oxfordshire is lower than the average for clinical commissioning group (CCG) regions in England.[12]

Nevertheless, the analysis presented here has significant strengths. A population-based approach was taken to include all patients who, at the time of the study, were being tested and monitored in primary care over time, allowing the authors to determine the population to which the NICE guidance is applicable. Standardised creatinine assays were used by the laboratory from 2008 until 2014 so there would be very little variation over time in laboratory methods. In addition, the CKD-EPI formula was used to calculate eGFR, in keeping with the most recent recommendation from NICE.

Comparison with existing literature

To the authors' knowledge, there has been no other attempt to quantify the need for cystatin C testing in a contemporary patient population undergoing renal function testing by GPs. Furthermore, there has been very little published on the barriers to implementing current NICE guidance for CKD in primary care.

Implications for research and practice

Cystatin C testing is only provided in a small minority of clinical chemistry laboratories in the UK at present, which represents a significant barrier to implementing the diagnostic algorithm of the new NICE guidance for primary care. Nationally, this means that there are large numbers of patients whose CKD status cannot be determined according to current NICE guidance on the diagnosis and management of CKD.

This inability to meet a national recommendation raises a major issue for GPs because they could be seen to fail their patients, according to this NICE criterion of optimal assessment of renal health. However, this is due to a lack of access to a diagnostic test, the availability of which was not mandated by NICE prior to the release of the guidance. This exemplifies a general problem that arises when guidelines are released without prior assessment of the practical requirements for their implementation. There are strategies that can minimise this problem; notably, the Nederlands Huisartsen Genootschap (NHG, or Dutch College of General Practitioners) has a well-established programme of producing evidence-based guidelines with education and professional development, alongside ensuring that there is adequate access to the investigations that are recommended. This Dutch strategy of developing guidance with close involvement of primary care physicians would identify where lack of access to diagnostics would limit adherence to evolving guidance

CCGs should identify how best to commission diagnostic services to help GPs implement NICE guidance to ensure accurate diagnosis and monitoring of CKD in their registered populations.

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Ethical approval

Ethical approval was not required. Aggregate anonymised laboratory data were accessed only by the clinical laboratory team as part of National Institute for Health and Care Excellence guidance readiness assessment.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

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