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PRACTICE

UNCERTAINTIES PAGE

What is the best glomerular filtration marker to identify people with chronic kidney disease most likely to have poor outcomes?

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the Cochrane Library. This paper is based on a research priority identified and commissioned by the National Institute for Health Research's Health Technology Assessment programme on an important clinical uncertainty. To suggest a topic for this series, please email us at uncertainties@bmj.com

Introduction

Glomerular filtration rate (GFR) is widely regarded as the best overall measure of kidney function. In recent years, the importance of this measure has increased as it has been incorporated as the primary criterion in an international classification system for kidney disease.[1] Routine availability of GFR estimates has improved recognition of chronic kidney disease,[2 3] but knowledge of GFR alone is insufficient to predict the risk of adverse outcomes in patients. Concern exists that not all people with decreased GFR, especially those without albuminuria, are at increased risk of adverse outcomes related to chronic kidney disease.[4] This may cause unnecessary alarm to patients and waste healthcare resources. Outcomes of importance in chronic kidney disease include progressive loss of kidney function (including kidney failure), acute kidney injury, cardiovascular events, complications related to progression of chronic kidney disease, and mortality. Earlier studies concentrated on the relative accuracy of estimated GFR (eGFR) compared with "true" GFR.[5] However, absolute accuracy in GFR estimation may not be the prime criterion, and some more recent literature has focused on the relative ability of different equations and markers to predict disease progression and poor outcomes.

GFR is measured using reference procedures that follow the renal clearance of an infused exogenous substance (such as inulin). However, these methods are cumbersome, impractical, and too costly for widespread use. Clinical laboratories report eGFR by using equations based on measurement of serum creatinine concentration, taking into account other variables including age, sex, and ethnicity. Laboratories use various equations to estimate GFR. Although perhaps not of primary interest to most requesting clinicians, the choice of equation can affect both the prognostic power and the accuracy of the GFR estimate. The Modification of Diet in Renal Disease (MDRD) Study equation has been widely used since 2000 to estimate GFR, but most evidence suggests that the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine based GFR estimating equation has superior accuracy,[5] and this equation is increasingly endorsed for use globally.[1 6 7] Equations incorporating cystatin C (a small protein filtered by the kidney), an alternative marker, either alone or in combination with creatinine, have also been proposed for estimating GFR.[8] Costs of cystatin C measurement are approximately 10-fold higher than those for creatinine. However, cystatin C based estimated GFR (eGFR-cystatin C) may have advantages over creatinine based estimates (see below), and some guidelines have started to recommend its use.[1 7] Clinicians therefore need to understand when eGFR-cystatin C may be useful. Other GFR and risk markers (for example, β-trace protein, symmetric and asymmetric dimethylarginine) are the focus of new research.

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What is the evidence of the uncertainty?

What is the best test to predict kidney failure and mortality in chronic kidney disease patients?

The ability to predict future adverse outcomes in patients with chronic kidney disease would allow interventions to be focused on those most likely to benefit and patients at low risk to be reassured. Pragmatically, risk prediction and consequent management of chronic kidney disease patients is likely to depend largely on use of laboratory generated GFR estimates, in addition to albuminuria. Whether the most accurate GFR estimates are also the best risk predictors is a matter of debate, as is how different measures of GFR could be combined to optimise management of patients.

A meta-analysis of data from 1.1 million adults showed the CKD-EPI-creatinine equation to be a better discriminator of future risk (mortality and kidney failure) than the MDRD equation.[9 10] The National Clinical Guidelines Centre recently considered the question "What is the best combination of measures of kidney function and markers of kidney damage to identify people with chronic kidney disease who are at increased risk?"[7] Medline, Embase, and the Cochrane Library were searched for English language articles. Data from three large prospective cohort studies[11-13] confirmed that CKD-EPI-creatinine based eGFR significantly improved risk prediction for kidney failure, acute kidney injury, heart failure, cardiovascular disease, coronary heart disease, and mortality compared with the previously used MDRD Study equation.[7]

An increasing body of evidence has confirmed the superior ability of cystatin C to predict poor outcomes compared with creatinine based eGFR. A meta-analysis of data from 16 studies including more than 90 000 participants found that use of cystatin C in addition to creatinine predicted risk of kidney failure and death more accurately.[14] These observations have been confirmed in other large scale studies in general and disease populations.[11 13 15-17] Increasing cystatin C concentration predicts increased risk independently of GFR.[18] This phenomenon (improved predictive ability over and above any improvement in GFR estimation) has been attributed to (as yet undefined) non-GFR determinants of serum cystatin C concentration that predict outcome.[19] Cystatin C based GFR estimation has been proposed as a useful confirmatory test of chronic kidney disease associated risk in the largest identified group of patients with chronic kidney disease (that is, those with GFR between 45 and 59 mL/min/1.73 m^2 and no albuminuria).[1 7] Little evidence relates to risk prediction in older people, the group with the highest prevalence of chronic kidney disease.

What is the best way to detect change in GFR (kidney disease progression)?

Clinicians monitoring a patient commonly look for a decrease in GFR that signals a decline in kidney function. The rate of decline is linked to likelihood of requirement for renal replacement therapy (dialysis or transplantation) and risk of morbidity and mortality. Most work to date has looked at the accuracy of GFR estimation in cross sectional studies. No prospective longitudinal data assess the relative abilities of GFR estimating equations to detect change in underlying measured GFR, which is probably of greater importance than accuracy at the level of the individual patient. Although one large retrospective study that assessed the accuracy of GFR estimating equations compared with measured GFR over time in people with kidney disease concluded that GFR estimating equations accurately reflect changes in measured GFR over time,[20] an earlier study found the opposite.[21] Neither study included GFR estimates derived using cystatin C.

Furthermore, a tension exists between what nephrologists consider to be a clinically significant change in GFR and what can reasonably be detected as a significant change on the basis of tests of GFR, taking into account the influences of biological and analytical variation. A relatively crude but widely used measure has been doubling of serum creatinine, corresponding to an approximate halving of GFR, but this is insufficiently sensitive to be useful in clinical practice. Guideline groups have proposed other definitions of progression,[1 7] but all are problematic.[22] From studies of biological variation, one can calculate that estimated GFR must change by more than 14% between two results for that change to be considered "true" with 95% certainty.[23] This is greater than annual changes in GFR observed in longitudinal studies in people known to have progressive disease.[22 24]

Contributors to the insensitivity of estimated GFR to detect progression are the biological variability of both blood creatinine concentration and underlying true GFR itself,[23 25] coupled with the fact that not all progression of chronic kidney disease is linear.[26 27] Whether cystatin C concentration has lower or higher biological variability than creatinine is uncertain.[23] If it is lower, GFR estimating equations based on serum cystatin C concentration may have higher sensitivity for detecting change in GFR at an individual level. No evidence exists to guide monitoring frequencies in management of chronic kidney disease; current recommendations are based on consensus opinion.[7]

Is ongoing research likely to provide relevant evidence?

We searched databases, including the World Health Organization International Clinical Trials Registry Platform (ICTRP), the European Union Clinical Trials Register, Clinicaltrials.gov, and the International Standard Randomised Controlled Trial Number (ISRCTN), for active longitudinal studies assessing the accuracy of GFR estimation in adults by using the terms "glomerular filtration rate" or "cystatin". We found only one relevant study. The eGFR-C study (ISRCTN42955626) is a multicentre prospective cohort study that will assess the ability of creatinine and cystatin C based estimates of GFR to detect changes in measured GFR over a period of three years in 1300 people with moderate chronic kidney disease.[23] The study has power to detect differences in the abilities of the GFR estimating equations to detect change in measured GFR in the cohort overall but insufficient power to assess such differences in racial and disease subgroups. It will collect long term outcome data but has not been powered to assess relative predictive equation performance in this context (see box). The FORM-2C study (http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=15514) is a cohort study in 1200 patients in general practice, assessing optimal monitoring frequencies of kidney function tests (personal communication).

What should we do in the light of the uncertainty?

No single method of GFR estimation is optimal across all levels of kidney function and in all disease settings. Few data exist to enable assessment of the performance of GFR equations in individual patients over time. More than one type of GFR estimate may be needed to optimise assessment. Clinicians should request creatinine based estimated GFR and urinary

albumin:creatinine ratio for general detection and monitoring of chronic kidney disease.[28] On the basis of increasing evidence of the superior ability of cystatin C to predict poor outcomes, guidelines recommend using cystatin C to assess risk in people with mild to moderate chronic kidney disease (GFR 45-59 mL/min/1.73 m^2 confirmed on at least two occasions more than 90 days apart) and no albuminuria.[1 7] Measure cystatin C once, when such patients are identified, to enable risk stratification. eGFR-cystatin C below 60 mL/min/1.73 m^2 confirms the presence of chronic kidney disease, whereas a value of 60 mL/min/1.73 m^2 or higher refutes the diagnosis. Partly owing to increased costs, cystatin C measurement outside this population and repeated measurements within this group are not recommended. Base frequency of monitoring on recent consensus based guidance, with significant change being regarded as that exceeding normal biological and analytical variation.[1 7] NICE also recommends tailoring frequency of monitoring according to factors such as the cause of chronic kidney disease, comorbidities, intercurrent illness, changes in treatment, and whether patients have chosen conservative management.[7]

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Recommendation for further research

Among people with chronic kidney disease, which glomerular filtration marker(s) can improve prediction of future adverse outcomes compared with current creatinine based estimates of glomerular filtration rate?

Population: People with chronic kidney disease (CKD)

Subgroups: Older people (75 years and older), black and minority ethnic people, people at high risk of developing CKD (for example, people with diabetes, hypertension, or cardiovascular disease or those recovering from acute kidney injury)

Measurement and comparators: Estimated glomerular filtration rate (GFR) and albuminuria; subgroups CKD-EPI, cystatin C, other markers; stratified by GFR category and albuminuria category

Outcomes: Mortality (all cause and cardiovascular), hospital admission, cardiovascular disease, progression of CKD, acute kidney injury, complications of CKD, patients' safety (serious adverse events), health related quality of life

Covariates: Sex, hypertension, and diabetes