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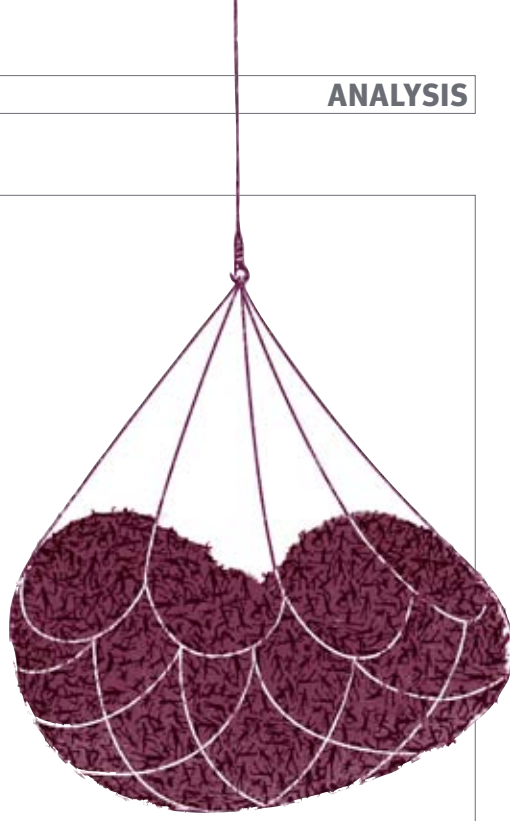
CHRONIC KIDNEY DISEASE How expanding definitions are unnecessarily labelling too many people as diseased



This article is part of a series on overdiagnosis looking at the risks and harms to patients of expanding definitions of disease and increasing use of new diagnostic technologies

In 2002 the United States Kidney Foundation launched a novel framework for defining and classifying chronic kidney disease.[1] The framework was widely embraced because it imposed order in a chaotic landscape characterised by a variety of names, including renal insufficiency, renal impairment, and renal failure. It has had an appreciable effect on clinical care worldwide through guidelines,[2] pay for performance measures,[3] and sparked debate on the merits of screening programmes.[4] However, it has also generated considerable controversy.[5-7] We examine the rationale for the framework, the varying responses and controversies it has provoked, and provide advice for clinicians who are being faced with an increasing number of people categorised as having chronic kidney disease.

SUMMARY BOX

Clinical context—Concern about the late presentation of kidney disease and missed opportunities for earlier intervention

Diagnostic change—A novel framework defining and classifying "chronic kidney disease" (CKD) introduced in 2002 and modified in 2012, based largely on laboratory measurements of kidney function and damage

Rationale for change—Identifying chronic kidney disease early would slow progression towards total kidney failure and provide an opportunity to prevent associated illness, particularly cardiovascular disease

Leap of faith—Identifying, monitoring, and treating the newly described chronic kidney disease will improve survival and quality of life

Increase in disease—The new definition labels over 1 in 8 adults (around 14%) as having chronic kidney disease. Before 2002 the lack of a consistent definition made prevalence estimates unreliable, but one US study suggested a figure of 1.7% of the population.

Evidence of overdiagnosis—The combination of the large numbers now labelled as having chronic kidney disease with low rates of total kidney failure suggest many of those diagnosed will never progress to symptomatic forms of kidney disease

Harms from overdiagnosis—Psychological effect of a disease label and the burden and costs of repeated assessment, testing, and potentially unnecessary treatment

Limitations—Lack of prospective data evaluating the benefits and harms of testing for, monitoring, and treating the early stages of chronic kidney disease

Conclusions—Clinicians should be sceptical about the current definition of chronic kidney disease and cautious about labelling patients, particularly older people

Changes in definition and diagnostic criteria

Two centuries ago Bright's description of the associations between kidney disease and albumin in the urine of patients with dropsy was hailed as one of the first practical modern aids to diagnosis. Starting with Homer Smith in the 1930s, estimates of "renal clearance" emerged as measures of kidney function, leading most recently to the development of equations using various serum biomarkers, such as creatinine or cystatin C, for estimating the glomerular filtration rate (GFR).

The 2002 framework uses the term "chronic kidney disease" to include conditions that affect the kidney, with the potential to cause either progressive loss of kidney function or complications resulting from decreased kidney function. Chronic kidney disease was defined as the presence of kidney damage or decreased kidney function for three months or more, irrespective of the cause.[1] It relies largely on two laboratory measures: an estimate of glomerular filtration rate (eGFR) based on serum creatinine or cystatin C levels and an assessment of kidney damage, derived from a range of tests, most commonly increased albumin in the urine (albuminuria). A single threshold for eGFR, <60 ml/min/1.73 m^2 uncalibrated for age or sex, was arbitrarily adopted to define chronic kidney disease. Similarly, ≥3 mg albumin/mmol creatinine in a random urine sample identified albuminuria. Initially, the framework set out five stages of chronic kidney disease, largely based on eGFR, ending with total kidney failure or end stage renal disease. Modifications followed, with 2012 guidelines dividing stage 3 (eGFR 30-59 ml/min/1.73 m^2) into 3A (30-44 ml/min/1.73 m^2) and 3B (45-59 ml/min/1.73m^2) and adding three extended categories for persistent albuminuria (fig 1).[8] These are in line with previous changes made in the classification adopted by the National Institute for Health and Care Excellence (NICE) in the UK.[2]

Rationale for change

The stimulus for the 2002 framework was the absence of an agreed definition and classification of kidney disease and evidence that people were experiencing avoidable harm through late

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presentation of serious kidney disease, including disproportionate numbers of African Americans[4] and the Australian aboriginal community.[9]

A key rationale for the new definition arises from evidence showing decreased eGFR and albuminuria are associated with increased risk of death or end stage renal disease.[10] The CKD Prognosis Consortium, an international research group, conducted a meta-analysis of published data from over two million people and concluded that "measures of kidney function and damage are independently associated with mortality and end stage renal disease regardless of age across a wide range of populations."[10] A second and related rationale comes from meta-analyses showing that reduced eGFR or albuminuria were consistently associated with cardiovascular mortality.[11 12]

The assumption was made that earlier identification and treatment could slow, stop, or reverse progression towards end stage renal disease.[1] The 2002 guidelines stated that treating early chronic kidney disease is "effective in slowing the progression toward kidney failure," with optimism largely directed at patients with more severe forms of specific kidney diseases manifested by marked proteinuria or rapidly declining eGFR.[1] A decade later, however, the National Kidney Foundation website stated that a suite of claims about benefits of early detection and treatment of generic chronic kidney disease "remains to be proven in appropriately powered randomized trials."[13] Similarly, the US Preventive Services Task Force, which recently found there was insufficient evidence to recommend general population based screening, reported that although identifying and treating chronic kidney disease may affect outcomes for people with established specific conditions, including diabetes or hypertension, there were no studies on the benefits of early treatment in people without them.[4]

Who developed the framework?

The framework was drawn up and published in 2002 by the Kidney Disease Outcomes Quality Initiative under the auspices of the US National Kidney Foundation. The guideline that launched the framework was supported by a pharmaceutical company.[14] In the face of confusion and criticism of the potential for the framework to lead to overdiagnosis, specialist international meetings were held in 2004, 2006, and 2009 to discuss modifications. In 2012 new guidelines reaffirmed the key elements of the 2002 guidelines, with modifications including dividing eGFR based stage 3 into 3A and 3B subcategories and formally adding three extended categories for albuminuria to the diagnostic matrix.[8] Nine of the 16 working group members who produced the 2012 guidelines declared financial ties to drug or device companies, though they stated every effort was taken "to avoid any actual or reasonably perceived conflicts of interest."[8] The body responsible for developing the guidelines has disclosed funding from a consortium of pharmaceutical or device manufacturers, though not for the "development of specific guidelines."[8]

Effect of framework on disease prevalence

Although it has long been recognised that kidney function declines with age and differs for men and women (fig 2), the threshold eGFR chosen to define disease was set at 60 ml/min/1.73 m^2, about half that of the normal level of a young adult.[8] Under the 2002 framework anyone with an eGFR below 60 ml/min/1.73 m^2 for three months or longer can be diagnosed as having chronic kidney disease stage 3A or greater, irrespective of their age or sex and even if they have no other overt signs of kidney damage, such as moderate or severe albuminuria.

The adoption of this definition has resulted in more than 1 in 8 adults (almost 14%) in the US being labelled as having chronic kidney disease[8 15] and as many as 1 in 6 adults in Australia.[16] Before the 2002 framework, estimates of prevalence varied widely depending on which threshold and definition was being used. For example, one study published in 2001, which used abnormal serum creatinine values (adjusted for sex) persisting for three months or more in people enrolled in a health maintenance organisation, estimated that 4.2 million Americans (1.7%) had chronic kidney disease.[17]

GFR categories (mL/min/1.73 m^2)			Persistent albuminuria categories			
			A1	A2	A3	
			Normal to mildly increased	Moderately increased	Severely increased	
			<3 mg/mmol	3-30 mg/mmol	>30 mg/mmol	
G1	Normal or high	≥90	55.6	1.9	0.4	57.9
G2	Mildly decreased	60-89	32.9	2.2	0.3	35.4
G3a	Mildly to moderately decreased	45-59	3.6	0.8	0.2	4.6
G3b	Moderately to severely decreased	30-44	1.0	0.4	0.2	1.6
G4	Severely decreased	15-29	0.2	0.1	0.1	0.4
G5	Kidney failure	<15	0.0	0.0	0.1	0.1
			93.2	5.4	1.3	100.0

Fig 1 | Prevalence of chronic kidney disease in the US by 2012 classification. Data on 18 026 adults from the National Health and Nutrition Examination Survey 1999-2006. Values in cells do not total to values in margins because of rounding. Green=low risk (if no other markers of kidney disease, no CKD), yellow=moderately increased risk, orange=high risk, red=very high risk. Reproduced with permission[8]

SUGGESTIONS FOR CLINICIANS

- Be informed about the controversy and debate over methods used to define chronic kidney disease
- Share uncertainty about appropriateness of diagnostic thresholds and reliability of measurements with patients
- Look for other changes that support the diagnosis—for example, is there evidence of anaemia, abnormal urinalysis results, or abnormalities on renal ultrasonography?
- Be aware of the variability in measures of kidney function (eGFR and albuminuria) and the need to repeat the test to confirm reduced renal function
- Don't routinely use the label chronic kidney disease for people aged 65 years and older with eGFR stage 3A and no albuminuria
- Older people with stable but modestly reduced eGFR (45-59 ml/min/1.73 m^2) are unlikely to have a high risk of future adverse events unless they have persistent overt albuminuria

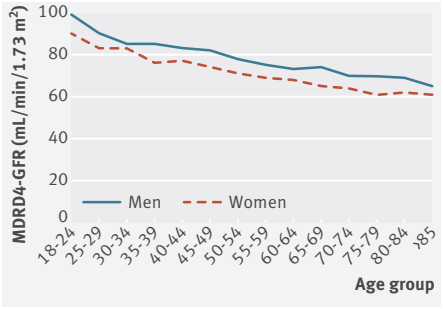

Fig 2 | Median eGFR rates for healthy white men and women by age. Redrawn with permission[5]

At least a third of the people who meet the new definition of chronic kidney disease are classified as stage 3A.[8] Most of them are older than 65 years of age, with more women than men, and many will have an eGFR that falls within the normal range (5th to 95th percentile) for their age.[5] Around three quarters of these have no urine markers of kidney damage, such as albuminuria.[18]

Response to the framework

The chronic kidney disease framework has been adopted by groups in many countries including the United States, Australia,[19] and the United Kingdom.[2]

One organisation has made substantial modifications to the framework. Kaiser Permanente in Southern California has adapted the framework using a formula to take age into account,[20] reducing the prevalence of chronic kidney disease in its insured population to about 3% compared with the almost 14% estimate arising from the framework definition.

Evidence of overdiagnosis

The use of a single threshold of an eGFR of 60 ml/min/1.73 m^2 without calibrating it for age or sex means that around half of people aged 70 years or more are being labelled or at risk of being labelled as having chronic kidney disease.[21] However, Dutch researchers have shown that an eGFR of 60 ml/min/1.73 m^2 is "within the normal reference range" for men over 60 years and women over 50 years and "cannot be used to define a diseased population."[5]

Advocates of the definition claim that "early detection can help prevent the progression of kidney disease."[22] But while 1 in 8 adults in the US may now be labelled as having chronic kidney disease, only around 1 in 3000-5000 are being newly treated for end stage renal disease each year.[15] In a study in a Norwegian county published in 2006, which surveyed 65 000 members of the general population with a median age of 49 less than 1% of people with an eGFR of 45-59 ml/min/1.73 m^2 (stage 3A disease) went on to develop end stage renal disease after eight years of follow-up.[23] Based on this, it is estimated that thousands of people with stage 3A disease may need to be treated to prevent one case of end stage disease,[24] raising questions about opportunity costs to health systems. A systematic review of screening and treatment concluded that although some treatments reduced the risk of end stage renal disease in selected patients with chronic kidney disease, "many of these patients may already warrant treatment with these therapies regardless of CKD status."[25]

Although early detection might benefit some people, by labelling so many people at low risk of symptoms as having chronic kidney disease, the new definition axiomatically produces overdiagnosis: "like a fishing trawler it captures many more innocent subjects than it should."[26] The current definitions may misclassify at least 30% of elderly people as having stage 3 disease,[18] with those classified as stage 3A without albuminuria at highest risk of overdiagnosis.

Concern among primary care physicians and specialists

Primary care doctors have expressed concern about the framework (*Inside Health*, BBC Radio 4, 15 August 2012),[24] and a qualitative research study conducted in a representative group of general practitioners and practice nurses across England found nearly all had "reservations as to whether CKD was really a disease," with some expressing concern about the medicalisation of the ageing process and the attendant potential for unintended harm.[27] The website of the United Kingdom National Kidney Foundation, a charitable patient organisation, explains that "Often CKD is only a very slight abnormality in the kidneys" and that "many of the elderly people with CKD may . . . have normal ageing of their kidneys."[28]

Uncertainties about what the evidence shows

Acknowledging concern about the risk of overdiagnosis, proponents have continued to defend the use of an eGFR threshold of <60 ml/min/1.73 m^2 to define chronic kidney disease by referring to the meta-analyses showing its associations with end stage renal disease and cardiovascular and all-cause mortality.[10-12] Although these analyses provide complex and important evidence, they are open to differing interpretations.[29,30] Some argue that the meta-analysis of data on end stage renal disease "neither supports nor refutes" the use of the 60 ml/min/1.73 m^2 threshold uncalibrated for age and sex for delineating chronic kidney disease.[31]

In relation to the associations with cardiovascular disease, questions remain about the extent to which a diagnosis of chronic kidney disease—as currently defined—adds meaningfully to the traditional assessment of risk,[32,33] and whether these associations justify current laboratory based thresholds to diagnose chronic kidney disease. Firstly, in terms of uncertainty, estimations of such associations have important limitations, including establishing appropriate reference points for comparisons, problems with standardising measurement, and a lack of a uniform protocol across study cohorts.[11,12] Secondly, some studies suggest that the designation of chronic kidney disease may not meaningfully add to the predictive ability of traditional cardiovascular risk factors.[33-35] For example, Angelantonio and colleagues found the clinically relevant incremental gain provided by chronic kidney disease was "about a sixth that provided by history of smoking."[33]

Uncertainties about the reliability of laboratory measurements

Although new estimating equations have improved the precision and reliability of eGFR measurements, problems with inaccuracy remain.[21] This is one reason why the framework requires that abnormal measurements persist for three months or more.[7] However, because eGFR levels can change over time, it is likely that many people would not be categorised as having chronic kidney disease if a longer period were required before diagnosis. A Norwegian study involving measurements from over 38 000 patients suggests that if the definition of disease required that an abnormality persists for 12 months, this could reduce the prevalence of stage 3 disease by 37%.[7]

There is also uncertainty about what concentration of albumin in the urine constitutes clinically "meaningful" kidney damage and how levels contribute to increased risk of future adverse events. Moderate albuminuria (defined as a urine albumin to creatinine concentration ratio of 3-30 mg/mmol (30-300 mg/g) and formerly known as microalbuminuria) is not pathognomonic of persisting chronic kidney damage. It can be transitory and is affected by

many extraneous factors, including high fever, vigorous exercise, smoking, obesity, medications, and diet.[36] A third of people who are identified as having kidney damage on the basis of moderate microalbuminuria may shed that label when re-tested up to two months later.[37]

Potential harms from overdiagnosis

The United States Preventive Services Task Force identified the most important potential harm of screening as "Patients could be falsely identified as having CKD and receive unnecessary treatment and diagnostic interventions."[4] Management of early disease mostly consists of tight management of blood pressure, and as the task force has pointed out the potential benefits of identifying and treating people at risk of cardiovascular disease through any screening programme for chronic kidney disease have to be weighed against the harms from the side effects of drugs and the risk of bringing blood pressure to excessively low levels.[4] In addition there is concern about the adverse effects of labelling healthy and asymptomatic people as having chronic kidney disease.[24 27 38] Studies of hypertension suggest that more disease labelling could increase psychological distress, absenteeism from work, and decrease quality of life.[39]

Cost implications

More routine reporting of kidney function since the advent of the 2002 framework has substantially increased specialist referrals for chronic kidney disease, with referrals up 60% within a single NHS trust covering a population of 560 000 people, according to a University of Cardiff study,[40] and up 40% in two hospitals in Brisbane, Australia.[41] In the United Kingdom general practitioners have been asked to form registers of those with chronic kidney disease and monitor people. An analysis of the cost and benefits of moving to reporting eGFR in routine blood analyses by den Hartog and colleagues found a far higher number of patients falsely diagnosed with chronic kidney disease and that "any small benefit in cost effectiveness was offset by potential adverse consequences of incorrectly diagnosing CKD."[42]

How to do better

It is not clear that the current markers of early renal dysfunction, either eGFR or microalbuminuria, are useful in identifying those patients who are at most risk of symptomatic renal disease. Further research is needed to better identify which patients are at greatest risk of a modifiable form of chronic kidney disease that without intervention would progress to symptomatic advanced disease. Until better methods are available, we suggest that clinicians consider the age of the patient and the trajectory of eGFR or urinary albumin test results, and acknowledge to patients that at the moment it is uncertain whether mildly reduced renal function in the absence of other risk factors should be treated or not (box). If a patient is found to have reduced renal function on a single test, the current guidance to confirm the result with another test soon after the first and that another test should be conducted after three months, should be followed.

Conclusions

The benefits, harms, and costs of testing, monitoring, and treating the increased number of people being identified as having chronic kidney disease need to be established by prospective studies. Meanwhile the risk of overdiagnosis warrants greater professional scrutiny and more public awareness. Clinicians should be careful not to apply disease labels to the many older people whose eGFR falls within the definition of chronic kidney disease but who are at very low risk of developing clinical problems. The fact that Kaiser Permanente explicitly attempted to avoid labelling "low risk elderly" people and adopted a higher threshold reinforces the argument for reviewing the 2012 framework. A review should be conducted by a panel with broad representation from specialty and primary care, population health, patient organisations, and civil society with minimal conflicts of interest. It is in everyone's interest to find the best way to maximise prevention of kidney disease and its consequences while minimising the risks and cost of overdiagnosis.

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Contributors and sources: RM is a writer and is currently doing a PhD on overdiagnosis, for which chronic kidney disease is a case study. RJG is a retired academic nephrologist who has written extensively about the pitfalls of diagnosing CKD. JD is a clinical epidemiologist and practising general practitioner.
Competing interests: JD and RM have received support from an NHMRC STEP grant, and are helping to organise the preventing overdiagnosis conference, supported by BMJ and Consumer Reports. RM has been advising on the BMJ Too Much Medicine series. RJG provides consultation to a number of pharmaceutical companies, none directly involved in providing care for end stage renal disease. He is a medical adviser to American Renal Associates, a US provider of dialysis. He also receives honorariums for engaging in educational activities for the American Society of Nephrology and UpToDate (a Wolters-Klewer Company).
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ANSWERS TO ENDGAMES, p 38

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CASE REPORT Stroke in a young man

1 Strokes can be ischaemic or haemorrhagic. Ischaemic strokes are broadly classified as embolic or arterio-occlusive. Haemorrhagic stroke is divided into parenchymal (superficial or deep) and subarachnoid, depending on the anatomical site of the bleed.
2 Classic homocystinuria (cystathionine β-synthase deficiency).
3 Any patient with suspected classic homocystinuria should have an initial screen to measure total plasma homocysteine, total plasma amino acids, serum vitamin B_{12}, and folate concentrations. In classic homocystinuria, total plasma homocysteine and methionine concentrations are raised.
4 Pyridoxine, betaine, protein restricted diet, treatment of coexisting vitamin B_{12} and folate deficiency and antiplatelet agents for recurrent thromboses.

ANATOMY QUIZ Axial T1 weighted magnetic resonance imaging of the female pelvis

A: Right acetabulum
B: Left sartorius muscle
C: Rectum
D: Greater trochanter of left femur
E: Right obturator internus muscle

STATISTICAL QUESTION Kaplan-Meier survival analysis: types of censored observations

The censored observations of the primary outcome are best referred to as right censored (answer *c*).