Cost-effectiveness analysis: cystatin C testing in the diagnosis of CKD

Methods

Model overview

Estimated glomerular filtration rate (eGFR) is an estimate of kidney function routinely used in clinical practice because measuring GFR (mGFR) is impractical and costly. An eGFR of less than 60 mL/min/1.73m^2 on at least 2 occasions separated by >90 days defines Chronic Kidney Disease (CKD) stage 3 and below. Current practice in the UK is to estimate GFR from serum creatinine (SCr) using the isotope dilution mass spectrometry (IDMS) related MDRD (Modification of Diet in Renal Disease) equation.

The use of a marker of kidney damage (urinary albumin:creatinine Ratio, ACR) is also routinely used in clinical practice. The finding of an elevated urinary ACR (≥3 mg/mmol) defines CKD when the eGFR is ≥60 mL/min/1.73m^2 and refines the classification of CKD regardless of kidney function, providing prognostic information at any level of eGFR.

The use of a universal threshold eGFR of 60 mL/min/1.73m^2 for the diagnosis of CKD in the absence of markers of significant kidney damage has been a source of controversy since the international 5 stage classification of CKD was first introduced. This is partly driven by the increasing inaccuracy of the estimating equations at higher GFR levels. Derivation of a newer estimating equation based on the CKD Epidemiology Consortium creatinine equation (CKD-EPI$_{creat}$) equation, has improved the accuracy of estimated GFR. Measurement of an additional marker of kidney function, cystatin C, has also been suggested to better define CKD using the CKD-EPI cystatin C equation (CKD-EPI $_{cys}$), or a combined equation using creatinine and cystatin, the CKD-EPI $_{creat-cys}$. It is proposed that use of these equations, particularly in the GFR range 45-59 mL/min/1.73 m^2, leads to more accurate diagnosis of CKD. Therefore the trade-offs are represented by the cost of the additional cystatin C measurements versus the cost of misdiagnosed patients (false positives) who are unnecessarily labelled as CKD and placed in a CKD management programme.

A significant number of patients will be affected by the choice of equation (~7% prevalence of CKD stages 3-5 in the general population using QICKD data). The guideline update literature review found no new evidence since the publication of CG73 on the cost-effectiveness of eGFR equations for this topic. As a consequence, the GDG has identified this topic as a high priority for an original economic analysis.

Comparators

Three diagnostic strategies for patients with suspected CKD (CKD-EPI$_{creat}$ 45-59 and ACR <3) were devised to allow for differential use of diagnostic tests.

The strategies compared are:

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- CKD-EPI$_{creat:}$ In this strategy, no further testing is conducted and the person is diagnosed as having CKD stage 3a.
- CKD-EPI $_{cys}$: In this strategy, eGFR is re-calculated using serum cystatin C and the CKD-EPI$_{cys}$ equation.
- CKD-EPI$_{creat-cys}$: In this strategy, eGFR is re-calculated using serum cystatin C and serum creatinine and the combined CKD-EPI equation.

After reviewing the clinical evidence it was decided unnecessary to consider the MDRD equation since CKD-EPI$_{creat}$ has both greater precision and less bias and is no more costly to administer.

Population

People with suspected CKD (CKD-EPI$_{creat}$ eGFR 45-59 mL/min/1.73 m^2 and ACR <3), categorised into the following subgroups.

- Adults 75+ years of age
- Adults under 75 years of age
  - With and without hypertension

Time horizon, perspective, discount rates used

The time horizon was one year in the base case. The perspective was that of the UK NHS.

Outcomes

The main outcomes of the model are:
- Proportion of patients falsely diagnosed as having CKD (False positive - FP)
- Proportion of patients falsely diagnosed as not having CKD (False Negative - FN)
- NHS cost at 1 year

Deviations from NICE reference case

QALYs were not calculated. The GDG decided that the key outcome would be false positives avoided (not QALYs). This is because:
- Most people, especially older people, who are eGFR 45-59 mL/min/1.73 m^2 will not progress to later stages of CKD
- Although we use a GFR cut-off to diagnose CKD, kidney function is a continuum and therefore (before disease has progressed) the FP, TP, FN, FP will have (almost) identical quality of life.
- It was agreed that a substantial proportion of FNs would be picked up by re-screening before significant disease progression.

Given the main outcome selected by the GDG was the number of FPs avoided, it was agreed that cost savings should be estimated over a short time horizon 12 months. This means that the cost savings associated with cystatin C are conservatively estimated. This was subjected to sensitivity analysis.

Approach to modelling

The model is a simple decision tree that categorises patients according to diagnostic outcomes (false positive (FP), true negative (TN), false negative (FN), and true positive (TP) results) – the model structure is presented in Figure 1.

Model inputs

Diagnostic accuracy data

The GDG requested data from studies in the guideline review for patients with CKD-EPI$_{creat}$ 45-59 mL/min/1.73 m^2 and ACR<3mg/mmol. Data was sought from studies that contained both CKD-EPI$_{creat}$ and CKD-EPI$_{creat}$. Data was received from the following studies:

- CKD-EPI derivation and validation cohorts (Inker 2012).
  - Age<75 Hypertension, No diabetes (n=142)
  - Age>75 No hypertension, No diabetes (n=150)
- Kilbride et al (2013)
  - Age 75+ (n=81)

Since there was little data for older patients, this was supplemented with unpublished data from the AGES-Reykjavik study (Inker 2013), provided by the authors of the CKD-EPI study.

- Age 75+ (n=156)

As indicated for the younger cohort we were able to sub-divide between those with and without hypertension and the few patients with diabetes were excluded. For the older cohort few patients did not have hypertension and a substantial proportion did have diabetes but the numbers were too small to allow further disaggregation.

The data is shown in Table 9. The individual results of the two 75+ cohorts are not presented because some of the data is academic in confidence. However, we can confirm that the prevalence, sensitivity and specificity across those two cohorts were very similar, suggesting that aggregation is not unreasonable.
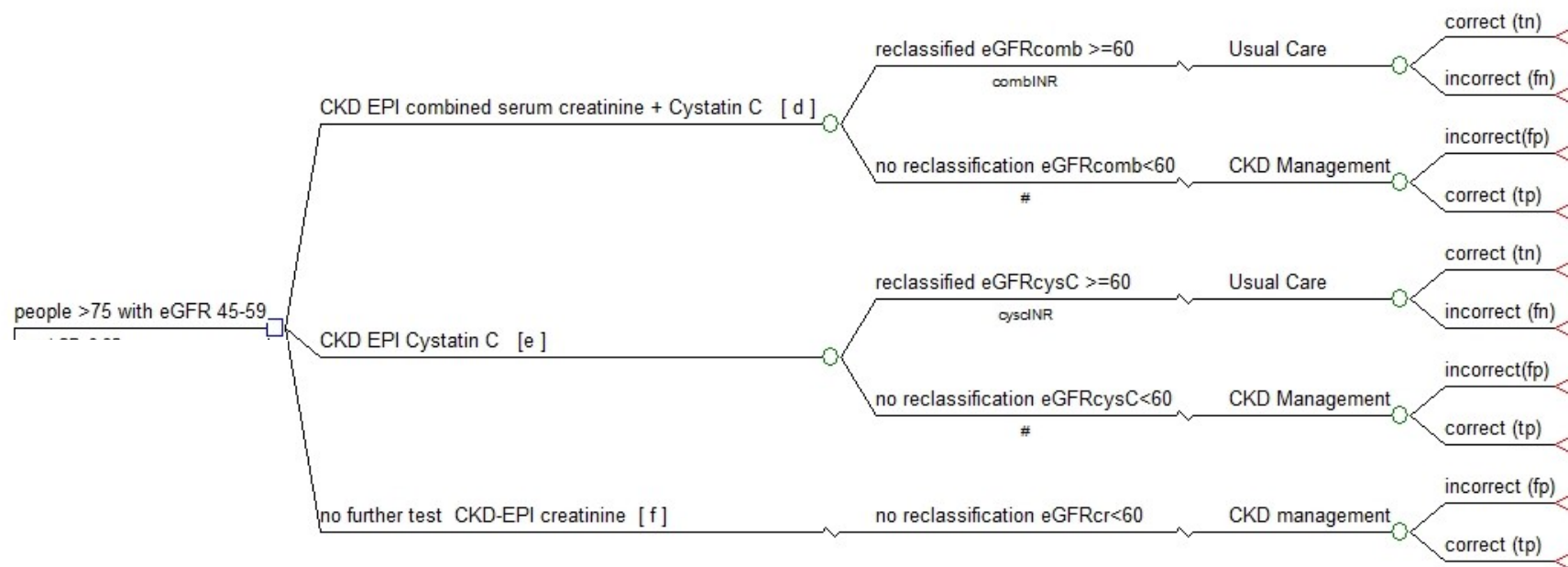
Figure 1: Decision Tree

Table 9 Diagnostic data

Age 75+

CKD-EPI$_{cys}$				NO. of CD	CKD-EPI $_{creat-cys}$				NO. of CD
	mGFR<60	mGFR>60		183		mGFR<60	mGFR>60		192
TP	160	25	FP		TP	173	29	FP	
FN	29	23	TN		FN	16	19	TN	
Total	189	48	237		Total	189	48	237	

Age<75 No hypertension

CKD-EPI $_{cysC}$				NO. of CD	CKD-EPI $_{creat-cys}$				NO. of CD
	mGFR<60	mGFR>60		113		mGFR<60	mGFR>60		121
TP	83	20	FP		TP	96	25	FP	
FN	17	30	TN		FN	4	25	TN	
Total	100	50	150		Total	100	50	150	

CD=correct diagnoses, FN=false negative, FP=false positive, TN=true negative, TP=true positive.All mGFR values are measured in mL/min/1.73 m^2

Resource use and cost

Diagnosis

In the base case it was assumed that the cystatin C test is requested at the same time as the confirmatory creatinine test, 3 months after the first abnormal eGFR reading. Manpower, equipment and storage costs for the different strategies were considered equal and excluded from this analysis. In terms of resources required, the only difference between GFR estimation methods is the chemical reagent required for the laboratory analysis. Due to the lack of published information on the costs of diagnostic tests, the GDG estimated that the cost of a serum creatinine reagent was £0.25 and serum cystatin C reagent was £2.50.

In sensitivity analysis we looked at alternative scenario where the cystatin C test was ordered after the results of the confirmatory creatinine test are known. In this scenario there are no costs associated with the CKD-EPI$_{creat}$ strategy and for the other strategies we allocated the full cost of a serum creatine test assumed to be £3 plus another £3 for phlebotomy (SA3 and SA4).

Since there will be a number of false negative results from both cystatin C strategies, in a sensitivity analyses we added a re-test at 12 months including a test (£6) plus a 10 minute GP visit (£37) for patients who were classified as not having CKD (SA1 and SA4).

CKD management

The components of CKD management are described in Table 10. The unit costs of these components were taken from standard sources. Patients categorised as CKD-EPI$_{cys}$ eGFR >60 mL/min/1.73 m^2 or CKD-EPI$_{creat-cys}$ eGFR >60 mL/min/1.73 m^2 do not incur these CKD management costs. They only accrue diagnostic test costs. No additional costs were assumed for false negative patients.

Drugs

It was hypothesised that people with CKD and hypertension might receive more intensive anti-hypertensive therapy. We conducted a comparison of antihypertensive costs for patients with (eGFR 45-59 mL/min/1.73 m^2) and without CKD (eGFR 60-89 mL/min/1.73 m^2) using data from general practice[329]- Table 11. The Drug and CKD management costs were estimated only for one year in the base case. However, in a sensitivity analysis, they were assumed to continue for 5 years (SA2). The annual cost of antihypertensive medication was lower by 15% (£7.00) in the group with eGFR 60-89 ml/min/1.73 m^2, which is probably an under-estimate since CKD patients might also be on higher doses of individual drugs.

Table 10: Annual Incremental cost of CKD management

Component	Unit Cost	Annual frequency	Source
GP visit 10 mins	£37.00	1	PSSRU 2012
GP nurse visit 10 mins	£7.50	1	PSSRU 2012
Biochemistry test	£3.00	1	NHS Reference Costs 2011-2012
Haematology test	£1.00	1	NHS Reference Costs 2011-2012
Phlebotomy	£3.00	1	NHS Reference Costs 2011-2012
Total cost	£51.50		

Table 11: Cost of antihypertensive medication

	Unit cost*	Patients with eGFR 45-59 ml/min/1.73 m² (n=7,993)		Patients with eGFR 60-89 ml/min/1.73 m² (n=25,001)		Assumption*	
Angiotensin-converting-enzyme inhibitor	£ 16.57	4884	61%	14263	57%	Weighted average of ramipril 10mg/day, lisinopril 20mg/day, perindopril erbumine 4mg/day	
Diuretic	£ 11.47	5056	63%	12374	49%	bendroflumethiazide	2.5 mg daily
Calcium channel blocker	£ 12.78	4271	53%	12410	50%	amlodipine	5 mg once daily
Beta blocker	£ 15.38	4032	50%	9787	39%	bisoprolol	10mg daily
Angiotensin receptor blocker	£ 40.71	2322	29%	6083	24%	Weighted average of irbesartan 150mg/day, candesartan 4mg/day, losartan 50mg/day	
Alpha blocker	£ 11.99	1391	17%	3551	14%	doxazosin	1 mg daily
Drugs per patient			2.15		2.34		
Weighted average cost			£ 46.10		£ 39.10		

* Source : National Drug Tariff 2012, Prescription Cost Analysis England 2012.

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Computations

Diagnostic Outcomes

For each equation patients were subdivided according to their estimated

	mGFR<60	mGFR>60
eGFR<60	True positive (TP)	False positive (FP)
eGFR>60	False negative (FN)	True negative (TN)

All GFR values units are ml/min/1.73 m²

Using this data, we calculated the following:

Prevalence=$TP + FN / (FN + FP + TN + TP)$ [*Same for all equations*]

Specificity= $TN / (TN + FP)$

Sensitvity= $TP / (FN + TP)$

Diagnostic odds ratio (DOR)= $\dfrac{TP/FN}{FP/TN}$

For the probabilistic analysis we calculate

TP=Sensitvity x prevalence

FN=(1-sensitvity) x prevalence

TN=Specificity x (1-prevalence)

FN=(1-specificity) x (1-prevalence)

Where the specificity, prevalence and DOR are each defined by a distribution (see Uncertainty, below) and the sensitivity is defined as:

Sensitvity= $1 \Big/ \left(1 + \dfrac{1}{DOR\left(\frac{1-specificity}{specificity}\right)}\right)$.

Costs

TP, FP=Test cost+drug cost+CKD management cost

TN, FN=Test cost only (+Re-test cost in sensitivity analysis)

Uncertainty

The base case model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input

parameter which was varied. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution. The model was run 10,000 times for the base case analyses and results were summarised.

We checked for convergence by plotting incremental cost on a graph for the probabilistic base case analysis. The incremental costs had converged by the 500th iteration.

The way in which distributions are defined reflects the nature of the data, so for example probabilities were given a beta distribution, which is bounded by zero and one, reflecting that a probability cannot be outside of this range. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 12: Description of the type and properties of distributions used in the probabilistic analysis

Parameter	Type of distribution	Properties of distribution
Prevalence of 'true' CKD Specificty Probability of being on a drug	Beta	Bounded between 0 and 1. Alpha=pN Beta=(1-p)N Where p=sample probability and N=sample size (For specificity N=the number of true neatives plus false positives in the sample)
Natural log of the diagnostic odds ratio (DOR)	normal	The DOR is bounded at zero. The mean of the distribution=ln(DOR). The standard error is defined as: $$SEln(DOR) = \sqrt{\frac{1}{TP} + \frac{1}{FN} + \frac{1}{TN} + \frac{1}{FP}}$$

Prices were left deterministic (that is, they were not varied in the probabilistic analysis). The sensitivity is calculated as a function of the DOR and the specificity, which captures the inverse relationship between sensitivity and specificity.

In addition sensitivity analyses were undertaken to test the robustness of model assumptions. These sensitivity analyses were conducted deterministically (that is, based on the parameter point estimates rather than their distributions). In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results.

Table 13: Prevalence and accuracy by cohort

	Prevalence	Sensitivity of eGFR CKD-EPI$_{cys}$	Specificity of eGFR CKD-EPI$_{cys}$	Sensitivity of eGFR CKD-EPI$_{creat-cys}$	Specificity of eGFR CKD-EPI$_{creat-cys}$
Age 75+	80%	85%	48%	92%	40%
Age<75 No hypertension	67%	83%	60%	96%	50%
Age<75 Hypertension	70%	80%	76%	85%	64%

Table 14: Base case results (probabilistic)

	Diagnostic outcomes			Mean costs (£)			
	Correct	FP	FN	Diagnosis	Additional drugs	CKD Care	Total
Age75+							
CKD-EPI$_{creat}$	79.8%	20.2%	0%	0.25		51.50	51.75
CKD-EPI$_{cys}$	76.6%	10.6%	12.9%	2.75		39.88	42.63
CKD-EPI$_{creat-cys}$	80.5%	12.2%	7.3%	2.75		43.60	46.35
Age<75 No hypertension							
CKD-EPI$_{creat}$	67%	33%	0%	0.25	0	51.50	51.75
CKD-EPI$_{cys}$	75%	13%	12%	2.75	0	35.36	38.11
CKD-EPI$_{creat-cys}$	81%	17%	3%	2.75	0	41.55	44.30
Age<75 Hypertension							

	Diagnostic outcomes			Mean costs (£)			
	Correct	FP	FN	Diagnosis	Additional drugs	CKD Care	Total
CKD-EPI_{creat}	70%	30%	0%	0.25	7.00	51.50	58.75
CKD-EPI_{cys}	79%	7%	14%	2.75	4.43	32.62	39.80
CKD-EPI_{creat-cys}	79%	11%	11%	2.75	4.93	36.29	43.97

FP=false positive, FN=false negative

Table 15: Base case results - incremental results (probabilistic)

| | False Positives | | | False negatives | | | Cost (£) | | |
| | Incremental vs CKD-EPIcreat | | | | Incremental vs CKD-EPIcreat | | | | Incremental vs CKD-EPIcreat | |
	%		lower 95%	upper 95%	%		lower 95%	upper 95%	Mean		lower 95%	upper 95%
Age75+												
CKD-EPIcreat	20.2%				0.0%				51.75			
CKD-EPIcys	10.6%	-9.7%	-13.8%	-6.3%	12.9%	12.9%	5.4%	24.4%	42.63	-9.12	-16.10	-4.05
CKD-EPIcreat-cys	12.2%	-8.0%	-11.8%	-4.9%	7.3%	7.3%	2.7%	15.7%	46.35	-5.40	-10.65	-1.80
Age<75 No hypertension												
CKD-EPIcreat	33.3%				0.0%				51.75			
CKD-EPIcys	13.3%	-20.0%	-26.9%	-14.0%	12.1%	12.1%	4.9%	23.5%	38.11	-13.64	-17.60	-9.88
CKD-EPIcreat-cys	16.7%	-16.6%	-23.2%	-11.1%	2.7%	2.7%	0.7%	5.7%	44.30	-7.45	-10.99	-4.41
Age<75 Hypertension												
CKD-EPIcreat	29.6%				0.0%				58.75			
CKD-EPIcys	7.0%	-22.5%	-29.6%	-16.1%	14.1%	14.1%	9.0%	20.2%	39.80	-18.94	-23.60	-14.39
CKD-EPIcreat-cys	10.6%	-19.0%	-25.7%	-13.0%	10.5%	10.5%	6.0%	16.0%	43.97	-14.77	-19.16	-10.56

Table 16: Sensitivity analysis (deterministic)

	Base case (probabilistic)	Base case (deterministic)	SA1	SA2	SA3	SA4
Age75+						
CKD-EPI$_{creat}$	51.75	51.75	51.75	257.75	51.50	51.50
CKD-EPI$_{cys}$	42.63	42.95	52.39	203.75	46.20	55.64
CKD-EPI$_{creat-cys}$	46.35	46.64	52.99	222.22	49.89	56.24
Age<75 No hypertension						
CKD-EPI$_{creat}$	51.75	51.75	51.75	257.75	51.50	51.50
CKD-EPI$_{cys}$	38.11	38.11	51.59	179.57	41.36	54.84
CKD-EPI$_{creat-cys}$	44.30	44.29	52.61	210.47	47.54	55.86
Age<75 Hypertension						
CKD-EPI$_{creat}$	58.75	58.75	58.75	292.74	58.50	58.50
CKD-EPI$_{cys}$	39.80	39.83	55.57	188.13	43.08	58.82
CKD-EPI$_{creat-cys}$	43.97	43.95	56.66	208.73	47.20	59.91

SA1=Sensitivity Analysis 1=The same as base case except that people that are CKD-EPI$_{cys}$>60 or CKD-EPI$_{creat-cys}$>60 are re-tested after 12 months incurring another test and a GP visit. SA2=Sensitivity Analysis 2= The same as base case except that CKD drug and management costs are for 5 years (not 1 year)
SA3=Sensitivity analysis 3=The same as base case except that cystatin C test is ordered after the result of the follow-up creatinine test
SA4=Sensitivity analysis 4=The same as SA1 except that cystatin C test is ordered after the result of the follow-up creatinine test

Results

The prevalence of 'true CKD' (mGFR<60 ml/min/1.73 m^2) was lower in the younger cohorts suggesting that the CKD-EPI creatinine equation is over-predicting CKD in these patients (Table 13). Sensitivity of the test was similar across the 3 cohorts but specificity was greater in the younger cohorts particularly in the hypertensive cohort, suggesting that the CKD-EPI creatinine equation is over-predicting in younger people much more so than the two cystatin-based equations. Across all 3 cohorts the combined equation was more sensitive but the cystatin C equation was more specific.

In all 3 cohorts, the cystatin c equation produced the fewest false positive results, which led to it being the lowest cost strategy – the cost of the test being more than offset by the subsequent reduction in drug and management costs (Table 14 and Table 15). In the cohort of older patients and the cohort of non-hypertensive patients, it was actually the combined equation that had the most accurate diagnoses since it had fewer false negative results due to its greater sensitivity.

If we consider CKD management costs over 5 years then the cost savings per patient tested compared with the creatinine test alone increase (Table 16) – for example, for younger patients without hypertension they increased from £14 to £78 per patient.

If we add the cost of a follow-up test (Table 16) to try and pick up false negatives after a year then CKD-EPI$_{cys}$ is the least cost strategy for younger patients but not for older patients. However, if we increase the timeframe of CKD management costs to 2 or more years then CKD-EPI$_{cys}$ is the lowest cost strategy for older patients as well.

If the cystatin C test is ordered after the results of the follow-up test are known (Table 16) then the CKD-EPI$_{cys}$ is the least cost strategy but not if there is a follow-up test to try and pick up false negatives after a year. However, again, if we increase the timeframe of CKD management costs to 2 or more years then CKD-EPI$_{cys}$ is the lowest cost strategy again.

Interpreting Results

Summary of results

Additional eGFR measurement for people with CKD-EPI$_{creat}$ eGFR 45-59 ml/min/1.73 m^2 is cost saving and reduces the number of false positives compared to eGFR measurement with serum creatinine alone for all subgroups investigated. However, additional GFR estimation using cystatin C or cystatin C + creatinine for people with CKD-EPI$_{creat}$ eGFR 45-59 ml/min/1.73 m^2 will also increase the number of false negatives identified.

Limitations and Interpretation

The GDG considered False Positives as the outcome of greatest concern because of the risks of medication and the unnecessary anxiety caused by over-diagnosis, which may have broader impacts on patients including life insurance premiums. The GDG assumed that False Negatives would not experience significant adverse effects as they would mostly be identified in the future according to other symptoms.

It would be difficult to estimate the longer-term cost and health impact of the different strategies, since this would depend on the progression of disease in the CKD negative patients (CKD-EPi$_{creat}$ 45-59 and CKD-EPI$_{creat\ cys}$=60+ and ACR,3) and how that progression is affected by CKD management, which we believe is not known with any precision. But it is acknowledged that this is a limitation of the analysis. However, it is perhaps not a serious one since most false negatives would be subsequently identified before significant progression especially if there is re-testing of CKD-negative patients after 12 months, as in

the sensitivity analysis. The analysis was assessed as partially applicable since it did not estimate quality-adjusted life-years.

The cost savings attributable to cystatin c testing were sensitive to some of the assumptions made. For example the addition of the cost of a re-test after 12 months to pick up patients previously given a false negative result meant that there were not net savings. But even in this scenario, when the conservative time horizon of 1 year was increased to 2 years then savings were apparent again. This means that re-testing at 1 year might be the optimal strategy. In the absence of re-testing at 1 year, the use of the CKD-EPI$_{creat-cys}$ equation could be considered a reasonable option being the most accurate test and with much of the cost savings of the CKD-EPI$_{cys}$ equation strategy. The analysis cannot definitively conclude which is more cost-effective CKD-EPI$_{creat-cys}$ or CKD-EPI$_{cys}$ since there is a trade-off between accuracy and cost.

The guideline's clinical review did not reveal strong evidence for differences in the relative accuracy of the different equations according to ethnicity or the presence of cardiovascular disease or diabetes or a history of acute kidney injury and therefore the findings of this analysis are likely to apply to all these subgroups. The cost savings we observed are only for people without diabetes. For those with diabetes, unless stage of CKD has significantly progressed, CKD management is unlikely to add to their NHS costs, since they will already be having regular contact with primary care and regular testing of kidney function. However, the GDG agreed that a separate diagnostic testing strategy for patients with diabetes would be confusing and therefore a single recommendation was made for all the comorbidity subgroups.

Evidence statement

One original comparative cost analysis found that CKD-EPI$_{cys}$ was less costly than CKD-EPI$_{creat}$ and CKD-EPI$_{creat-cys}$ for diagnosing CKD in people with CKD-EPI$_{creat}$45-59, ACR<3mg/mmol and without diabetes (magnitude of cost savings varied according to age group, comorbidity, time horizon and re-testing strategy). This analysis was assessed as partially applicable with minor limitations.