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Current evidence on screening for renal cancer

Juliet Usher-Smith[1], **Rebecca K. Simmons**[2], **Sabrina H. Rossi**[3], **Grant D. Stewart**[3]

[1]The Primary Care Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge CB2 0SR, UK

[2]Department of Public Health, Bartolins Allé 2, University of Aarhus, DK-8000 Aarhus C, Denmark

[3]Department of Surgery, University of Cambridge, Addenbrooke's Hospital, Cambridge Biomedical Campus, Hills Road, Cambridge CB2 0QQ, UK

Abstract

The increasing incidence of renal cell carcinoma (RCC), the high proportion of asymptomatic individuals at diagnosis and the high mortality rate, together with a recent promising cost-effective analysis, suggest that RCC meets some of the criteria for screening. Targeted screening of high-risk individuals is likely to be the most cost-effective strategy to maximise benefits and reduce the harms of screening. However, the size of the benefit of earlier initiation of treatment and the overall cost-effectiveness remains uncertain. There is also uncertainty about the optimal screening modality and target population, as well as the specification and implementation of a screening programme. Before moving to a fully powered trial of screening, future work should focus on: developing and validating accurate risk prediction models; developing non-invasive methods of early RCC detection; establishing the feasibility, public acceptability and potential uptake of screening; establishing the prevalence of RCC and stage distribution of screen-detected RCC; and, evaluating the potential harms of screening, including the impact on quality of life, overdiagnosis and over-treatment.

Introduction

After three decades of interest in the topic, there is now a developing body of research on screening for renal cell carcinoma (RCC). Internationally there is also great interest in evaluating the optimal strategy for earlier diagnosis of this 'silent' cancer [1–4], which is largely curable if identified at an early stage. A study on early detection and treatment of RCC was recently defined as one of the top research priorities by kidney cancer patients, caregivers and expert clinicians in two independent studies [1,3,4].

Author contributions

GDS and JUS conceived the idea for the paper. RKS wrote the first draft of the manuscript. All authors made substantial contributions to discussion of content and critically reviewed and/or edited the article before submission.

Competing interests

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The incidence of RCC is increasing worldwide, with the highest rates observed in developed countries [5]. Established risk factors for RCC include older age, male sex, smoking, hypertension and obesity [6]. The rising incidence of RCC is likely associated with increases in these risk factors and increases in incidental detection of malignancy via imaging for other complaints [5,7,8]. Sixty percent of all patients with RCC have asymptomatic disease and therefore many cancers are detected late [9]; over a quarter of individuals have evidence of metastases at diagnosis [10]. RCC is thus the most lethal urological malignancy; 50% of all patients developing the disease will eventually die from it [11]. Patients with stage four disease have a 12% five-year (age standardised relative) survival rate compared to 87% survival in patients with stage one disease (see Table One)[10].

The increasing incidence of RCC, the high proportion of asymptomatic individuals at diagnosis and the high mortality rate mean that RCC meets some of the criteria for suitability for screening. Early detection of asymptomatic RCC may downstage the disease, reducing the prevalence of later stage localised RCC (with high risk of recurrence/metastasis) and primary metastatic tumours and associated expenditure relating to systemic therapies such as sunitinib, pazopanib, axitinib, cabozantinib, nivolumab and ipilumimab. However, although the RCC community has considered the topic of screening for many years [12–14], there is no definitive study on the issue.

Here we present a balanced review of the potential benefits and harms of screening for RCC, outlining evidence to date, and concluding whether there is enough evidence to begin a clinical trial of renal cancer screening.

Evidence on screening for renal cancer

We evaluated the evidence on screening for RCC against the UK's National Screening Committee criteria [15]. These are based on the original criteria for screening proposed by Wilson and Jungner in the 1960s [16] but also include criteria relating to the effectiveness, acceptability and opportunity cost of the screening programme and implementation considerations. The results are outlined in Box One and summarised below.

Condition

RCC is an important health problem. It is the 9th most common cancer in men and 14th commonest cancer in women worldwide [5]. The increasing incidence, poor survival rates and high proportion of asymptomatic patients make it a good candidate for consideration of screening.

The best available information on the prevalence of undiagnosed asymptomatic RCC is a meta-analysis of five series of middle-aged Americans who received CT screening (n=16,174; mean age range, 58 to 64 years; 61% male) [17]. The prevalence of asymptomatic RCC in these studies ranged from 0.11% to 0.76%; the pooled prevalence was 0.21% (95% confidence interval, 0.14-0.28%). Current estimates of prevalence in the UK, for example, are extrapolated from studies in the US or Japan [17,18]. The only study reporting RCC prevalence by age and gender derives from a Japanese population screened with ultrasound

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from 1983 to 1996 [14]. The prevalence of renal masses and RCC in studies from Europe and North America are more than double those in studies from Asia [18].

The “sojourn time” or “preclinical period”, which is defined as the time during which an individual has RCC but has not yet received a diagnosis and therefore during which a screening programme may intervene, is estimated to be between 3.7 and 5.8 years in an asymptomatic screening population [17]. This period is long enough to provide a window for screening but also not too long a duration to suggest that screening would only detect conditions that would not progress to a clinical diagnosis nor impact on the individual during their lifetime.

Whether detecting RCC during the preclinical period benefits individuals is less clear as illustrated by data obtained over the last four decades. The incidence of RCC has steadily risen over the past 30 years [19]. This is thought to be due to a combination of a true increase in incidence resulting from risk factors in the general population (such as the rise in obesity and aging population) and an increase in diagnosis of early stage disease through the widespread use of abdominal imaging. As a consequence of the growth in abdominal imaging, there has been a stage migration with an increasing number of earlier stage tumours detected [20]. Treatment rates have increased in parallel with incidence and overall 5-year survival has also increased [21]. However, from the 1980s to 2008, improved treatment and 5-year survival rates did not appear to translate into improvements in mortality rates: SEER data shows that while RCC incidence was rising, RCC mortality remained static [19,22]. This phenomenon of “treatment disconnect” has been attributed to length and lead-time bias and the observation that, despite the increase in stage I cancers, there has not been a concomitant reduction in the incidence of stage II-IV disease [20]. However, since 2001 overall mortality rates in patients with RCC have declined and since 2012 deaths from RCC have been declining in tandem with plateauing incidence rates [19]. Artefacts relating to the SEER database, including missing data and allocation bias have also been shown to contribute substantially to the observed “treatment disconnect”[19,20,22].

As the established risk factors for RCC are similar for other chronic conditions, such as type 2 diabetes, cardiovascular disease and lung cancer, all cost-effective primary prevention interventions have been implemented as far as practicable. There are no known pre-malignant conditions which can be treated to prevent the development of RCC. As such, the only obvious mechanism of reducing deaths from RCC is by identification of the tumour at an early and treatable stage.

These observations further emphasise that, overall, the evidence in favour of screening on the basis of the condition is mixed and incomplete. The key questions will be: (i) whether screening will lead to a further increased detection of RCC and a further stage shift in disease, despite current high levels of imaging for other abdominal complaints[23], and ii) if screening leads to a RCC survival benefit, rather than just lead time bias. Further research is also needed to identify markers of aggressive disease and to refine treatment protocols such as active surveillance in order to ensure individuals do not undergo treatment for clinically insignificant tumours.

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Test

The ideal screening modality for RCC is yet to be elucidated. Urinalysis for non-visible haematuria is an inadequate screening tool as this approach suffers from low diagnostic yield and a high number of false positives and false negatives [24–26]. Several serum and urine biomarkers, such as KIM-1 in plasma and aquaporin/perilipin in urine, offer promising modes of detection but none have been validated in a large prospective cohort [6]. Developing accurate, inexpensive and non-invasive methods of RCC detection using blood or urine thus remains a research priority.

Abdominal contrast enhanced computed tomography (CT) is the gold-standard method of detecting a renal mass. CT would not be appropriate for national screening due to the relatively low prevalence of renal masses in the general population, cost, radiation dose and the increased potential for incidental findings [27]. However, while CT is not suitable as a screening modality for RCC alone, it may be possible to combine RCC scanning with other CT scan-based health check programmes. This approach has the potential to reduce costs and provide additional benefits to individual screening participants. Using non-contrast abdominal CT for simultaneous detection of aortic aneurysms and other abdominal malignancies is unlikely to be cost-effective [17,28–30]. However, it may be possible to extend low-dose CT scans now implemented in the United States for lung cancer screening and being trialled in lung screening and health check programmes in Europe to include the whole of the kidneys [31]. These lung cancer screening and health check programmes identify those at highest risk based on age and smoking. As these are the two risk factors most strongly associated with both lung cancer and RCC, this combined approach warrants further consideration. It would also allow the establishment of the sensitivity and specificity of low-dose CT scans for detecting RCC.

It may also be worth evaluating the possibility of stepped approaches in which only a subset of those invited to lung cancer screening would be offered the additional screening. The potential benefits in terms of numbers needed to screen would need to be balanced against the increased administrative and logistic complexities of this process.

Further behavioural research is also needed to address how the offer of additional testing within the context of other screening programmes would affect uptake. We recently examined data from a survey of 1,011 adults regarding several elements of screening for kidney cancer. We found that 962 (95%) participants said they would be ‘likely’ or ‘very likely’ to take up kidney cancer screening if they were offered that in addition to lung cancer screening, with only 2% reporting the additional invitation would make them less likely to attend for lung screening (unpublished data, 2019). There is also good evidence on the attractiveness of combined screening from the wider literature. In a survey of 1,562 adults in Australia, 85.3% (CI 81.9-88.2%) stated they would support a combined ‘One Stop’ cancer screening programme [32]. The decision to participate in one form of cancer screening has also been shown to positively influence the decision to participate in other forms of cancer screening, for example, associations between breast and cervical cancer [33].

For a standalone RCC screening programme, ultrasound scanning (USS) of the kidney has been proposed as a potential option [18]. Complete visualisation of the kidneys by USS occurs

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in 97.4% cases, compared with 98.8% visualisation rates of the aorta in AAA screening [34,35]. USS also has an excellent sensitivity (82–83.3%) and specificity (98–99.3%) for detecting RCC in the general population [36,37]. The tool is non-invasive, safe (no radiation exposure), quick (imaging of liver, gall bladder, pancreas, kidney, spleen and abdominal aorta takes 5-6 minutes on average[14]) and inexpensive. USS has successfully been used in abdominal aortic aneurysm (AAA) screening programmes in primary care with high attendance rates [34,35]. However, this must be tempered against the following negative points. Firstly, there is reduced USS accuracy with obesity, which is common in RCC patients. Secondly, USS accuracy is determined by lesion size. It has previously been shown that USS permitted detection of only 26% of CT-confirmed lesions less than 1 cm, 60% of lesions greater than or equal to 1 cm but less than 2 cm, 82% of lesions greater than or equal to 2 cm but less than 3 cm, and 85% of lesions 3 cm or more in size [38]. Thirdly, there is a need further investigation of USS identified renal masses and incidental findings using CT. Finally, as renal ultrasound is technically more challenging to perform than aortic ultrasound, it is unclear if scanning could be carried out by a technician or if a sonographer would be needed. The expertise and scan duration required to maintain high quality (practitioners must be audited and revalidated) would impact both accuracy and cost.

Several observational studies have suggested that there may be a survival benefit associated with early detection of RCC using ultrasound [6]. For example, a retrospective analysis of the results of 41,364 abdominal ultrasounds at a single institution in Japan showed that five-year survival was significantly better in an asymptomatic group of individuals diagnosed with RCC compared to symptomatic patients diagnosed with RCC (94.7 vs 60.9%, $p < 0.01$) [39]. However, more robust evidence in the form of a randomised controlled trial is needed to demonstrate whether screening for RCC is associated with improved survival or simply a lead time bias [6].

Intervention

The major hypothesised benefit of RCC screening relates to improved survival outcomes through earlier detection and treatment in the time between disease onset and clinical diagnosis. Tumours detected by incidental diagnosis are usually smaller in size and associated with improved survival compared to symptomatic tumours (independent of tumour grade and stage) [40,41]. Early diagnosis thus has the potential to optimise survival [42]. Detection of smaller tumours may also allow the use of minimally invasive techniques, reducing rates of open surgery and reducing morbidity and length of hospital stay [43]. However, any potential benefit can only be proven with a clinical trial which shows better outcomes for screened individuals compared with usual care.

Screening programme

Although the incidence of RCC increases with age, it would not be beneficial to screen very elderly individuals with potentially co-morbid conditions. The precise age range for screening will depend on the cost-effectiveness analysis of the eventual modality. Our cost-effectiveness analysis of USS showed that screening men aged 50-60 years was the most cost-effective approach [44].

As outlined above, there is currently no evidence from high quality RCTs that a screening programme for RCC would be effective at reducing morbidity and/or mortality. A recent modelling study suggested that a single round of USS screening for RCC compared to usual care among 60-year old males would be cost-effective, with an ICER~£18,000/QALY [44] (Table Two). The equivalent cost for 60-year old females was £37,000/QALY. The value of information analysis suggested that further research on this topic is economically viable and would be of value to society.

The results of the cost-effectiveness modelling are highly sensitive to the prevalence of RCC [44]. Indeed, one of the perceived barriers to population screening is the relatively low prevalence of the condition [18]. Targeted screening of high-risk individuals using established risk factors is, therefore, likely to be the most cost-effective strategy to maximise benefits and reduce the harms of screening [45–47]. There are a number of published risk prediction models for RCC based on lifestyle factors [48], single nucleotide polymorphisms (SNPs) [49] and blood- or urine-based biomarkers [50,51] that could potentially be used for this purpose. For example, among 925 asymptomatic individuals identified as high risk based on age (≥ 50 years), smoking (≥ 10 pack-year smoking history) and occupational carcinogen exposure (≥ 15 years exposure), ten patients were diagnosed with RCC at 6.5 years follow-up, giving a prevalence of 1.1%, which is nearly ten times higher than in unselected groups representing the general population [52]. Recent whole genome sequencing studies have revealed that the initial genetic events leading to the development of cancer start many years before a clinical diagnosis is made [53,54]. In ccRCC data analysis revealed that the initial genomic changes (3p loss) occurs in a few hundred cells in childhood/adolescence. The second VHL allele undergoes mutation 5-20 years later, following which a tumour develops over the subsequent 10-30 years [53]. It is possible that in the future screening programmes may also be able to target those individuals with these founding mutational events.

A screening programme is only effective though if people attend. A low awareness of the risk of RCC in the general population may impact on screening uptake if individuals do not consider themselves at risk and/or are not concerned about RCC. Risk stratification also adds a further dimension, particularly if the data on risk factors is not routinely collected. Research in the context of other cancer screening programmes has found that individuals are generally positive about potential risk stratification, but that they tend to be more resistant to less intensive screening (for low-risk individuals) than more intensive screening for those at high-risk [55,56]. As sex is a strong risk factor for RCC (with males at increased risk), using risk to determine eligibility for RCC screening would result in men, on average, being invited at younger ages than women. More research is needed to consider how to define high-risk groups, how to implement a risk-based RCC screening programme, and the public acceptability of such a programme.

An evaluation of a screening programme for RCC should also consider potential harms. In particular, there is a need to quantify the impact of screening for RCC on quality of life and whether screening is associated with a disutility [18] i.e. a reduction in quality of life due to a particular screening test or intervention. If the disutility associated with renal ultrasound screening is ≥0.05 for one week for 60-year old men, screening would no longer be cost-effective [44].

A further potential harm relates to the over-diagnosis of slow-growing small renal masses (SRM) that would never become clinically significant [57]. Most SRMs grow slowly or remain stable in size, with only up to one third exhibiting aggressive potential (rapid growth or doubling time < 12 months) [58,59]. Advances in our understanding of the natural history of SRMs [60] and biopsy proven small renal cancers will allow active surveillance with delayed intervention to reduce over-treatment. Prospective studies such as the European Active Surveillance of Renal Cell Carcinoma (EASE) study [60] will provide a better understanding of the natural history of the disease, which can inform the design of the screening intervention. However, such information would also need to be captured in a clinical trial of screening to demonstrate the potential impact of over-diagnosis. We also need to quantify the impact of incidentally detected benign renal lesions on patients and the health service. Due to the limited use of renal tumour biopsy, around 15-30% of small renal masses are found to be benign following surgical excision [61–63]. Advances in our understanding of the aetiology of these masses, better interpretation of renal biopsy, and novel urinary or serum biomarkers may reduce these rates in the future.

Implementation criteria

The clinical management of RCC is relatively well established and evidence-based guidelines are available [64]. It is not yet established whether patients should undergo surgery, cryoablation or active surveillance, although the NEphron Sparing Treatment (NEST) study is comparing percutaneous cryoablation with robotic partial nephrectomy in patients with biopsy-proven renal cell carcinoma [65]. There are ongoing trials on neoadjuvant and adjuvant therapy [66]. The outstanding implementation criteria outlined in Box One are yet to be addressed in the context of screening for RCC but could be developed following the results of a trial.

Patient perspective

Renal cancer patients have lobbied for a study on RCC screening for many years. Recent analyses confirm that patients consider screening as one of the major unmet research needs for this condition [1,3,4]. Indeed, following the results of their annual patient survey, which showed that 73% of those surveyed showed no signs of the disease before diagnosis, Kidney Cancer UK recently called on the government to support a national screening programme for RCC [67].

There is also enthusiasm from members of the public without a history of RCC. In a recent focus group led by us on the topic, participants considered RCC screening an important area of research, with several referring to friends or relatives who had been diagnosed with kidney cancer only as a result of other unrelated investigations. Important considerations from their perspective included the burden of testing, how the information and results would be communicated and the well-known challenge of identifying those with lower health literacy and of lower socio-demographic status who have the potential to benefit most but who often do not take-up opportunities for screening. They were generally comfortable with a stratified screening approach, although stressed the importance of the need for transparency about who is or is not being invited. A small number were concerned about

people who would not fit the risk profile but would go on to develop RCC. These are important considerations for any future research in this area.

Moving to a trial of renal cancer screening

We estimate that we would need to see ~300 deaths from renal cancer across a control and screening group to have 80% power to demonstrate a 25% reduction in deaths from RCC due to screening over a 5 year period as the majority of recurrences and deaths from recurrent kidney cancer will occur in that period following surgery [68]. Even with a risk-based strategy including only 60-70 year old smokers/ex-smokers for example, we would therefore need ~175,000 participants in both the screening and control cohort. Given the large number of participants needed for a definitive clinical trial, there remain a number of outstanding research priorities that must be considered first (Box Two). We suggest tackling these priorities in parallel using a phased approach before moving to a full trial.

Firstly, as the targeting of high-risk individuals is likely to be the most cost-effective screening strategy, more research is needed to develop and validate accurate risk prediction models that incorporate genetic and phenotypic risk factors, as is being done in other cancers [69–71]. Alongside this research, we need to accelerate the development of non-invasive methods of kidney cancer detection using blood or urine and validate them in large prospective cohorts [72,73].

Secondly, we need to establish the feasibility of the proposed screening delivery mechanism, examine potential uptake and acceptability of a risk-based programme, and quantify possible harms (including incidental detection of other lesions of unknown significance). In particular, the cost of screening ultrasound is a major determinant of cost-effectiveness [44], so further research into the cost and accuracy of renal USS for RCC is needed.

Thirdly, we should consider whether we can add RCC to screening for other conditions such as lung cancer or AAA. For example, embedding small feasibility studies within on-going lung cancer screening trials would enable assessment of the uptake and acceptability of the additional screening to members of the public and the additional time and logistical impacts on delivery. This would entail careful, considered collaboration between colleagues conducting such screening studies or ongoing programmes.

Finally, any research should also take into account whether screening can translate into a survival benefit relative to the current status quo of high rates of incidental diagnosis via the widespread use of abdominal imaging [74,75].

Conclusions

A growing body of evidence on RCC screening has been published. RCC currently meets many but not all of the criteria for screening. Targeted screening of high-risk individuals is likely to be the most cost-effective strategy to maximise benefits and reduce the harms of screening. However, the size of the benefit of earlier initiation of treatment and the overall cost-effectiveness remains uncertain. There is also uncertainty about the optimal screening modality and target population, as well as the specification and implementation of a

screening programme. Before moving to a full trial of screening for RCC, future work should focus on: developing and validating accurate risk prediction models; developing non-invasive methods of kidney cancer detection using blood or urine; establishing the feasibility, public acceptability and potential uptake of screening; establishing the prevalence of RCC and the stage distribution of screen-detected RCC; and, evaluating the potential harms of screening, including the impact on quality of life, overdiagnosis and over-treatment.

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Box One

Summary of the evidence on screening for renal cell carcinoma against the UK's National Screening Committee criteria

The condition

1. *The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease*.

Importance: RCC is the 9th most common cancer in men and 14th most common cancer in women worldwide [5]; 50% of all patients developing the disease will die from kidney cancer [11].

Incidence & prevalence: Half of all patients with RCC have asymptomatic disease and therefore many cancers are detected late [11]. The best available information on RCC prevalence is a pooled prevalence estimate of 0.21% (95% confidence interval, 0.14-0.28%) [17]. The incidence of RCC is increasing worldwide, with the highest rates observed in developed countries [5]. The global age-standardised incidence rate is 4.5 per 100,00 population [76].

Mortality: The global age-standardised mortality rate is 1.8 per 100,000 population [76].

Natural history: This is incompletely understood. All aggressive, lethal kidney cancers start as small renal cancers, but not all small renal cancers develop into aggressive life-threatening lesions. The lead-time for development of significant disease is unclear. The European Active SurveillancE of Renal cancer (EASE study) of prospective assessment of progression of small renal cancers will enable a better understanding [60]. However, it has been suggested that the "sojourn time" or "pre-clinical period," which is defined as the time during which an individual has RCC but has not yet received a diagnosis, is between 3.7 and 5.8 years, suggesting that most RCCs have a detectable preclinical period [17].

Risk or disease markers: There are a number of published risk prediction models for RCC based on lifestyle factors [48], single nucleotide polymorphisms (SNPs) [49] and blood- or urine-based biomarkers [50,51] that could potentially be used to identify individuals at high risk of RCC. There are well established and simple methods (i.e. lesion size) of determining the likely aggressiveness of kidney cancer [77].

2. *All the cost-effective primary prevention interventions should have been implemented as far as practicable*.

The established risk factors for kidney cancer are: male sex, smoking, hypertension, obesity, renal disease, alcohol intake and family history [6]. These risk factors are generic for many other diseases and as such general prevention strategies are in place.

3. *If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications*.

N/A. This document refers to sporadic kidney cancer, not familial kidney cancer linked to a series of genetic syndromes [78].

The test

4. *There should be a simple, safe, precise and validated screening test.*

For a standalone RCC screening programme, ultrasound scanning (USS) of the kidney may be the most appropriate test. Sensitivity and specificity are 82-83% and 98-99%, respectively; however, accuracy is dependent on tumour size [6]. The test is non-toxic and safe. It is not yet validated for high-throughput scanning in the context of screening. Nor is it determined if non-sonographers can deliver these scans.

It may be possible to extend low-dose CT scans now implemented in the United States for lung cancer screening and being trialled in lung screening and health check programmes in Europe to include the whole of the kidneys [31].

5. *The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.*

Any renal mass or anomaly (i.e. complex cyst, stone) would be reported.

6. *The test, from sample collection to delivery of results, should be acceptable to the target population.*

USS is a non-toxic, non-invasive technique. It is used in abdominal aortic aneurysm screening with 84-85% attendance rates [34,35], suggesting an acceptable test, with similar rates expected for RCC.

7. *There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.*

Well established diagnostic and management pathways are in place for renal masses and other anomalies identified.

8. *If the test is for a particular mutation or set of genetic variants the method for their selection and the means through which these will be kept under review in the programme should be clearly set out.*

N/A

The intervention

9. *There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered.*

The major hypothesised benefit of RCC screening relates to improved survival outcomes through earlier detection and treatment in the lead time between disease onset and clinical diagnosis. This can only be proven with a clinical trial which shows better outcomes for screened individuals compared with usual care. Detection of smaller

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tumours may also allow minimally invasive treatment techniques reducing rates of open surgery, and therefore, associated morbidity and length of hospital stay.

Wider benefits: Potentially problematic non-renal cancer lesions would be identified by USS scanning, such as renal stones and other renal lesions (upper tract urothelial cancer), which will likely benefit the individual to have identified at a pre-symptom stage.

10. *There should be agreed evidence based policies covering which individuals should be offered interventions and the appropriate intervention to be offered*.

These are relatively well established, using International guidelines such as the European Association of Urology guidelines [64].

The screening programme

11. *There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened*.

There is currently no evidence from high quality RCTs that a screening programme for RCC would be effective at reducing morbidity and/or mortality.

12. *There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public*.

Evidence not yet available.

13. *The benefit gained by individuals from the screening programme should outweigh any harms, for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications*.

Evidence not yet available.

14. *The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource*.

A recent modelling study suggested that a single round of USS screening for RCC compared to usual care among 60-year old males would be cost-effective, with an ICER~ £18,000/QALY [44]. The equivalent cost for 60-year old females was £37,000/QALY. The value of information analysis suggests further research is likely to be of good value to a funder.

Implementation criteria

15. *Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme*.

This is already the case, via evidence and guideline based practice [64].

16. *All other options for managing the condition should have been considered (such as improving treatment or providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available*.

These strategies i.e. neoadjuvant and adjuvant therapy are ongoing but have not yet shown a survival advantage [66].

17. *There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards*.

To be developed.

18. *Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme*.

To be developed, including evidence that ultrasound technicians can deliver the test.

19. *Evidence-based information, explaining the purpose and potential consequences of screening, investigation and preventative intervention or treatment, should be made available to potential participants to assist them in making an informed choice*.

To be developed.

20. *Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public*.

To be developed.

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Box Two

Outstanding research priorities in screening for renal cell carcinoma

1. Develop and validate accurate risk prediction models for RCC
2. Develop non-invasive methods of early kidney cancer detection using blood or urine
3. Establish the optimal screening modality and target population
4. Based on the findings from points 1 to 3, specify the design and implementation of a screening programme
5. Establish the feasibility, public acceptability and potential uptake of RCC screening
6. Establish the prevalence of RCC and the stage distribution of screen-detected RCC
7. Evaluate the potential harms of screening, including the impact on quality of life, overdiagnosis and over-treatment

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Table One

Kidney cancer five-year net survival by stage, with incidence by stage[1]

	Female		Male	
Stage	**Number of cases**	**Five-year net survival (95%CI)**	**Number of cases**	**Five-year net survival (95%CI)**
1	6,933	88.2 (86.5 to 90.1)	10,775	85.8 (84.0 to 87.6)
2	1,253	77.0 (72.7 to 81.5)	2,093	76.2 (72.3 to 80.3)
3	2,340	72.2 (69.1 to 75.5)	4,489	75.3 (72.9 to 77.8)
4	3,116	13.2 (11.5 to 15.0)	5,908	11.9 (10.5 to 13.5)
Unstageable	61	-	68	-
Unknown / missing	2,656	-	4,327	

[1]All data: adults diagnosed with kidney cancer (C64) in the UK 2013-2017, followed up to 2018.

Source: Cancer Research UK (n.d.) (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer)

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Table Two

The incremental costs (cost of screening and treatment), quality adjusted life years (QALYs) and incremental cost-effectiveness ratio (ICER) per person screened by age and sex. Reproduced with permission from Rossi et al[44]

	Males			Females		
	40 years	**50 years**	**60 years**	**40 years**	**50 years**	**60 years**
Prevalence of RCC	0.14% (0.08-0.23%)	0.23% (0.12-0.37%)	0.34% (0.18-0.54%)	0.07% (0.04-0.11%)	0.09% (0.05-0.14%)	0.16% (0.08-0.25%)
Incremental costs	£47.06	£45.69	£44.55	£47.61	£46.99	£46.56
Incremental QALYs	0.00155	0.00205	0.00246	0.000809	0.000937	0.00125
ICER	£30,367	£22,277	£18,092	£58,819	£50,160	£37,327