Risk-stratified screening for the early detection of kidney cancer

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Abstract

Earlier detection and screening for kidney cancer has been identified as a key research priority, however the low prevalence of the disease in unselected populations limits the cost-effectiveness of screening. Risk-stratified screening for kidney cancer may improve early detection by targeting high-risk individuals whilst limiting harms in low-risk individuals, potentially increasing the cost-effectiveness of screening. A number of models have been identified which estimate kidney cancer risk based on both phenotypic and genetic data, and while several of the former have been shown to identify individuals at high-risk of developing kidney cancer with reasonable accuracy, current evidence does not support including a genetic component. Combined screening for lung cancer and kidney cancer has been proposed, as the two malignancies share some common risk factors. A modelling study estimated that using lung cancer risk models (currently used for risk-stratified lung cancer screening) could capture 25% of patients with kidney cancer, which is only slightly lower than using the best performing kidney cancer-specific risk models based on phenotypic data (27%-33%). Additionally, risk-stratified screening for kidney cancer has been shown to be acceptable to the public. The following review summarises existing evidence regarding risk-stratified screening for kidney cancer, highlighting the risks and benefits, as well as exploring the management of potential harms and further research needs.

Introduction

The incidence of kidney cancer is increasing worldwide, and the global burden of the disease is projected to rise further in future [1,2]. Given the disease is often asymptomatic, late-stage diagnosis remains a key contributor to poor survival rates. Optimal management of localised kidney cancer partly through earlier detection and screening has therefore been identified as a future key research priority by independent international collaborations [3-8]. In the UK, earlier cancer detection is also a key component of the National Health Service (NHS) Long Term Plan for all cancer subtypes, aiming to increase the proportion of cancers detected early (i.e. stage I-II) from 50% to 75% by 2028 [9]. Population screening for kidney cancer was initially a topic of great research interest in the 1990s and early 2000s, with various simple and low-cost modalities being investigated including urinary dipstick and ultrasound [10]. Table 1 summarises screening tools which have been investigated to enable early detection of kidney cancer, highlighting that the ideal modality is yet to be determined. Meta-analyses have consistently estimated that between 1 and 3 cases of kidney cancer would be detected for every 1000 asymptomatic individuals screened using ultrasound or CT (pooled prevalence of kidney cancer 0.17% [95% CI, 0.09–0.27%] and 0.21% [95% CI, 0.14–0.28%] using ultrasound and CT, respectively) [11,12]. However, given this relatively low prevalence of kidney cancer, screening the general population was deemed inefficient and research efforts in this field were paused [10,13]. A health economic analysis confirmed that the prevalence of kidney cancer is a key determinant of cost-effectiveness and suggested that identifying populations with higher prevalence may be a key strategy to enable a viable screening programme [14]. A resurgence of interest in the topic of screening for kidney cancer has occurred over recent years, focusing on the possibility of targeted or risk-stratified

screening. Whilst untargeted population-level screening for kidney cancer has been the subject of previous reviews [10,15], this review represents a detailed summary of the existing evidence for risk-stratified kidney cancer screening.

Principles of risk-stratified screening

Several population-wide cancer screening programmes are currently implemented in the UK, including breast, cervical and colorectal cancer screening. However, any screening programme has the potential to harm both individuals and society, including: physical harm (resulting from both the screening test and/or follow-up procedures, which may be invasive, as well as overdiagnosis and overtreatment), psychological harm, financial costs, social harm, and opportunity costs to the health service [16]. Risk-stratified cancer screening may reduce harms for low-risk individuals, while improving early detection by targeting those at highest risk. Screening only high-risk individuals rather an unselected population could also maximise resource use, by increasing cancer detection whilst reducing the overall costs associated with screening. This potential improvement to the ratio of benefits and harms, has led stakeholders to investigate risk-stratified screening for established cancer screening programmes. For example, risk-stratified screening for breast cancer is a key agenda topic for NHS England [17,18]. Targeted screening using polygenic risk scores (PRS) may increase the efficiency (increase cancer detection and reduce cancer deaths) of existing breast and colorectal cancer screening programmes [19]. An independent review of adult screening programmes in England recommended that targeted screening should be given the same weight and funding commitments as those for population screening [20]. Most recently,

targeted screening for lung cancer has been formally recommended by the UK National Screening Committee [21].

Successful implementation of risk-stratified screening for kidney cancer would require an accurate risk prediction model which is feasible, cost-effective, acceptable to the public and deliverable in the current health care system. This would enable the identification of individuals deemed to be at high risk, who could subsequently undergo screening using one of a number of different modalities (such as plasma or urinary tests, ultrasound or CT) (Table 1). Risk prediction models for kidney cancer could include risk factors covering a range of data types, including phenotypic data (modifiable and non-modifiable risk factors for kidney cancer such as age, sex, family history), genetic data (including single-nucleotide polymorphisms; SNPs) or even biomarkers (measured in urine or plasma). Whilst some phenotypic data may be available through medical records (for example, basic demographic and medical history is available in primary care records), the inclusion of others (for example, information about lifestyle risk factors) would likely require the use of patient questionnaires. The use of biomarker or genetic data would require additional resources to collect and process samples, which would impact the feasibility of the screening programme and the resources required to implement within the health service.

Phenotypic and genetic risk models for kidney cancer

A number of individual risk factors for kidney cancer have been identified (including age, sex, smoking status, body mass index, hypertension, diabetes and family history of kidney

cancer), however individually these are each associated with a relatively low relative risk of developing kidney cancer (Table 2) [10]. Importantly, these risk factors are also associated with increased susceptibility to several metabolic, cardiovascular and other malignant conditions and are not specific to kidney cancer. It is therefore unsurprising that the search for a prediction model which is able to accurately identify those at highest risk of developing kidney cancer has been challenging, with model performance remaining relatively poor compared to other cancers with more specific risk factors (for example, lung or breast cancer).

In general, model performance in a population may be evaluated by assessing calibration (i.e., the model's ability to accurately estimate risk) and discrimination (i.e., how well a prediction model distinguishes between individuals with and without kidney cancer) in a representative cohort. The most widely used measure of discrimination is the area under the receiver-operating curve (AUROC) or c-statistic (these are equivalent for binary outcomes). The receiver-operating curve is used to plot sensitivity against 1-specificity for a range of cut-off points. An AUROC of 1 indicates that, in the cohort used to test the model, the model always assigns a higher score to any individual who goes on to develops kidney cancer than it assigns to any individual who doesn't develop kidney cancer. An AUROC of 0.5 indicates the model does not perform better than random chance or flipping a coin [22].

A systematic review [23] screened over 15,000 articles and identified 11 published risk prediction models for kidney cancer which reported performance measures; highlighting that whilst more than 50 models have been published, only a limited number report model performance (which is required for cross-study comparisons). The identified risk models

included combinations of phenotypic, biomarker and/or genetic data. The most commonly included phenotypic risk factors were age, sex, smoking status, and body mass index. Interestingly, hypertension and diabetes were not included in the risk-prediction models identified by the review, despite being considered established risk factors for kidney cancer (Table 2). Five models used biomarker data alone, though these were typically evaluated in studies limited by smaller sample sizes than the phenotypic models. Most of the models had acceptable-to-good discrimination, with reported AUROCs >0.7. However, in most cases performance was measured directly in the development population or in an internal validation (measuring performance in a resampled or split-sampled development population). Disappointingly, only two out of 11 models had been externally validated in populations distinct from their development cohorts, and both of these models included only phenotypic risk factors. Lack of external validation, low sample sizes (the majority of models were developed with a sample size <100), and high risk of bias were all identified and none of the models could be used in clinical practice without addressing these limiting factors. Therefore, Harrison et al. set out to externally validate 30 existing phenotypic risk prediction models using a cohort of more than 450,000 participants from UK Biobank, which included 635 cases of kidney cancer [24]. Ten models achieved reasonable discrimination in men (AUROC between 0.64 and 0.71), women (AUROC between 0.62 and 0.72) and in a mixed sex cohort (AUROC between 0.67 and 0.71). The best performing kidney cancer specific risk-prediction model, by Singleton et al. **[25]**, is described more in detail later in this review. Although model discrimination was modest, the best performing models for kidney cancer achieved a similar discrimination to risk prediction models for other cancer types in similar studies, such as colorectal cancer [26] and melanoma [27].

Harrison et al.[22] also performed a systematic review to identify risk prediction models which include genetic risk factors (with or without phenotypic risk factors) to predict kidney cancer, and externally validated 31 genetic models in the same UK Biobank cohort. The identified genetic models had mainly been developed to investigate a small number of SNPs with known causal pathways linked to kidney cancer (only one of which showed any discriminative ability in validation), however, eight PRS using larger numbers of SNPs determined through genome wide association studies (GWAS) were also identified. The best performing PRS had poor discrimination with an AUROC of 0.55 (95% CI: 95% CI 0.53–0.57) in this validation. Concordant findings were observed in a study by Kachuri et al. [28], which evaluated a PRS for kidney cancer as well as other cancer types, and measured the performance gain when these were added to simple phenotypic models. Genetic risk prediction models in kidney cancer performed worse compared to other cancer types. The best performing predictive model for kidney cancer which combined genetic and phenotypic data provided only a negligible gain in discriminative ability compared to a model using phenotypic data alone (an increase in the AUROC of 0.007 from 0.716 to 0.723). In summary, modifiable phenotypic risk factors had a larger impact on kidney cancer risk than genetic risk, and this was more pronounced than for other cancer types, consistent with previous studies. The relatively low performance of genetic models for kidney cancer reflects the infancy of this field compared to genetic risk prediction for other cancers. We note the limited number of GWAS studies which have been carried out to identify genetic variants associated with susceptibility to kidney cancer. Compared with the nine GWAS studies which have been used to develop the current set of PRS for kidney cancer, there have been >100 different breast cancer GWAS [29]. For example, Graff et al.[30] developed a PRS for kidney cancer that included 19 SNPs (the largest number identified in the review),

but developed models for other cancers that included much higher numbers of SNPs (for example, 187 SNPs in the colorectal cancer score) and which achieved much better performance when tested in the UK Biobank cohort. In future, following further GWAS, it may be possible to identify additional SNPs associated with kidney cancer and so improve the model performance.

Modelling studies to assess the potential impact of risk-stratified screening

Risk-stratified screening aims to reduce the number of unaffected individuals being screened, whilst maximising the number of cancer cases detected; thereby reducing the number of individuals who needed to be invited to screening to identify one kidney cancer case (NNI). However, depending on the criteria used and the threshold selected, restricting screening to individuals labelled as 'high-risk' can mean that the majority of cancer cases will still occur in individuals labelled as 'low-risk' who are not invited to screening. As with all screening programmes that are not offered universally from birth to all individuals, there will also inevitably be some cases of cancer that will be missed by the screening programme. A modelling study has estimated the expected outcomes of population screening versus risk-stratified screening, comparing age and sex based stratification to the use of the best performing kidney cancer risk-prediction models [24]. For population-based screening of both men and women aged >60 years, it is estimated that 227 individuals would need to be invited to screening to identify one kidney cancer case (NNI=227; 29% of the population are screened, which includes 49% of kidney cancer cases). A screening strategy based on both age and sex improved the NNI, but also correspondingly reduced the proportion of kidney

cancer cases expected to be identified; the NNI for screening all men aged >60 years was 206 (14% of the population screened, which includes 30% of kidney cancer cases). Using a phenotypic risk prediction model further improved the NNI compared to screening based on only age and sex, however the improvement was small (the best performing model gives an NNI of 180, with 12.3% of the population invited which includes 32% of kidney cancers). Looking at these scenarios more closely, at a risk threshold of 0.4% (i.e. individuals are invited to screening if the risk of developing kidney cancer is >0.4% over 6 years), all of the five risk models resulted in screening 11%-13% of the population and detecting 27%-33% of cases. Raising the risk threshold, and hence restricting screening to increasingly smaller but higher-risk groups, improves screening efficacy (reducing the NNI) but also decreases the proportion of total cancers that are included in the screened group. For example, a threshold of 0.7% is estimated to result in a NNI as low as 111 for one model, however only 2% of the population will be screened and only 8% of kidney cancer cases will be detected. While it is necessary that the discriminatory ability of any model used is sufficient to distinguish those at high-risk of kidney cancer, determining an appropriate risk threshold – which balances the number of people invited (minimising harms to those a low risk) while still identifying a large proportion of cases (improving rates of early detection) – is crucial to ensure the screening programme would be effective and efficient.

Huntley et al. performed a separate modelling study to compare risk-stratified screening using polygenic risk scores across cancer types [19]. PRS were used to stratify the general population into quintiles of risk, for various cancers. Using a PRS to screen individuals in the highest risk quintile for kidney cancer (i.e. 20% of individuals with the highest risk of kidney

cancer) would identify 22% of all kidney cancer cases [19]. This was lower than that for other cancers: screening the top PRS-defined high-risk quintiles would detect 37% of breast cancer cases, 46% of prostate cancer cases, 34% of colorectal cancer cases, 29% of pancreatic cancer cases and 26% of ovarian cancer cases. At present, the added cost and inconvenience associated with assessing genetic data suggests that it is preferable to consider utilising risk prediction models for kidney cancer which are based on phenotypic factors alone. In future, it may be plausible to offer the general population a single test (such as a cheek swab) to evaluate polygenic risk for numerous cancer types, with subsequent screening of high-risk individuals for specific cancers based on individual risk estimates.

Risk-stratified kidney cancer screening combined with other screening programmes

Given the low prevalence of kidney cancer, a number of alternative strategies have been investigated to enable combined screening of kidney cancer with other conditions which share common risk factors. Screening for kidney cancer alongside the existing aortic aneurysm screening programme (currently offered to men aged 65 years) has been proposed [14,31]. Another strategy involves offering screening for kidney cancer to individuals undergoing targeted lung cancer screening with CT. Such "combined screening" has potential cost-savings, as screening for kidney cancer could be offered as an add-on, and still represents "targeted screening" given individuals undergoing lung cancer screening are expected to also be at higher risk of kidney cancer. In 2022 the UK National Screening Committee recommended introducing a targeted lung cancer screening program across the

UK for people at high risk [21]. Members of the general public aged 55-74 who are current or ex-smokers are identified via GP records and will be offered an assessment of their lung cancer risk. A risk prediction score (such as The Liverpool Lung Project score version 2 (LLP) and the Prostate Lung Colorectal and Ovarian model 2012 (PLCO)) will then be used to determine individuals at high risk, who will be offered a low-dose chest CT. The Yorkshire Kidney Cancer Screening Trial (YKST), currently underway, is the first ever feasibility study of combined renal and lung cancer screening, whereby individuals undergoing low-dose chest CT as part of targeted lung cancer screening are offered an add-on non-contrast abdominal CT [32].

Two widely used lung cancer risk models, the LLP and PLCO risk models, assess age, sex, smoking history, family history of lung cancer, presence of COPD/lung disease, asbestos exposure, BMI, history of cancer; some of which also increase the risk of kidney cancer. The best performing kidney cancer specific risk-prediction model, by Singleton et al. [25], comprises the following risk factors: age, sex, BMI, smoking status, hypertension diagnosis, systolic and diastolic blood pressure. While it is well established that the LLP and PLCO have excellent discrimination for lung cancer, a recent modelling study showed that they also discriminate reasonably for kidney cancer [33]. The AUROC for predicting kidney cancer was 0.66 [0.64–0.68] for LLP and 0.62 [0.60–0.64] for PLCO, compared to an AUROC for predicting lung cancer of 0.82 [0.81–0.83] for LLP and 0.84 [0.83–0.85] for PLCO. As expected, these lung cancer risk models have lower discrimination for kidney cancer than the best kidney cancer specific model by Singleton et al. (AUROC 0.71 [0.69–0.73]) [33]. However, individuals offered lung cancer screening have 1.6x higher risk of developing kidney cancer than the general population [33], meaning the prevalence of kidney cancer is

enriched in this group. The same modelling study estimated that combined screening for lung and kidney cancer using the protocol from the YKST study could identify up to 25% of patients with kidney cancer (15% of the population invited for screening) [33], which is slightly lower than the expected proportion of cases that could be detected in a screening programme using kidney cancer-specific risk models (27%-33% of kidney cancers identified; 11%-13% of the population screened)[24]. Combined screening for lung and kidney cancer would, however, miss three quarters of kidney cancers (75%), including all cases arising in non-smokers. Comparatively, risk-stratified screening for lung cancer identifies 61% of lung cancer cases, with the high effectiveness in part due to the strong association between smoking and lung cancer and resultant high performance of the risk prediction models used [33]. In the absence of population screening for kidney cancer, once lung cancer screening is rolled out nationally, then combined lung and kidney cancer screening could be an efficient way of improving early detection rates of kidney cancer, with minimal additional resources required. There is significant potential for cost saving from a health service perspective with this add-on approach. Other potential benefits of this combined screening approach include: abdominal CT will also enable the identification of other serious abdominal conditions in addition to kidney cancer (such as aneurysms or abdominal malignancies), and increased convenience for patients compared to undergoing two separate screening tests. The results of the YKST feasibility trial, and accompanying health economic analysis are awaited and will inform whether such combined screening is a viable strategy. The potential imminent roll out of lung cancer screening to larger study populations across the UK means a full trial evaluating an add-on abdominal CT for renal cancer screening would be achievable.

Liquid biomarkers as an adjunct to risk-stratified screening

Liquid biomarkers have also been proposed as a promising novel strategy to aid cancer screening in future. Ideally, a biomarker test could be developed to be examined in the urine or blood of individuals, preferably delivered as a simple low-cost point-of-care test. This could stratify which individuals would then undergo targeted screening with more expensive tests (such as CT). Biomarker screening could be offered to the general public or to individuals considered at higher risk of cancer, based on age, sex or other risk factors. The most promising liquid biomarker thus far is circulating tumour DNA (ctDNA), small fragments of tumour-derived DNA containing mutations or methylation changes that can be identified in the plasma (or urine) of cancer patients and are absent in controls. ctDNA has been proposed as a pan-cancer screening tool, where individuals would undergo a single pan-cancer blood test, then undergo more targeted investigations depending on which tumour type of ctDNA was elevated [34-36]. However, relatively low levels of ctDNA are present in patients with kidney cancer compared to other malignancies, though the biology underpinning this is not yet understood. While promising results have been reported for most cancer types, sensitivity is much lower for kidney cancer (18.2% for kidney cancer stages I-IV and only 7.1% for stages I-II) [37], meaning a high proportion of RCCs would be missed (especially at the typically asymptomatic early stages), limiting use as a screening test [38]. Large scale studies evaluating pan-cancer screening using ctDNA are being undertaken in the NHS [39], and results regarding the early detection of kidney cancer will be particularly interesting. Pan-cancer screening using ctDNA, which could be offered to individuals at higher risk of cancer, is an attractive prospective warranting further research. However, this research is at a relatively early stage, and any application to screening

programmes (and in particular to kidney cancer where these early results have been less promising) remains a future prospect.

Public acceptability

A key requisite of any screening programme is that it should be clinically, socially and ethically acceptable to the public and the health service, and indeed this is one of the Wilson and Jungner screening criteria [40]. Acceptability is key to facilitating sufficient attendance at screening; and in the context of risk-stratified screening must be evaluated in terms of both the screening test used and the criteria (or risk-model) used to determine eligibility.

The importance of using an acceptable screening tool is exemplified by cervical cancer screening. Low uptake of cervical cancer screening (uptake approximately 69%)[41] has been found to be linked to the embarrassment and discomfort associated with a speculum examination [42]. Further, survey results suggest that greater intention to attend screening is associated with less perceived burden/inconvenience about the screening tests [43]. In a survey of over 1000 members of the general public, participants reported they would be more likely to attend kidney cancer screening if this involved a urine test, compared to a blood test or ultrasound [43]. Unsurprisingly, non-invasive methods such as a urine test were preferable to tests which involve a blood draw or ionizing radiation (e.g., a stand-alone CT scan of the abdomen), although overall intention to attend kidney cancer screening (regardless of the screening tests used) was very high. Combined screening of lung and renal

cancer was viewed very favourably by study participants, with higher intention to attend screening of that type than any of the other modalities, [43] suggesting convenience is highly valued by the public.

The method used to risk stratify individuals into high versus low risk must also be suitable to encourage screening uptake. In a recent discrete choice experiment the public were found to value the sensitivity of the risk stratification model (the proportion of cancers detected and not missed) much more than specificity (the number of people undergoing unnecessary investigations) [44]. Overall sensitivity was considered 7 times more important as an attribute than specificity. This suggests that the risk stratification model used must have a high sensitivity, and is consistent with the general literature that the public would rather undergo unnecessary tests to avoid missing cancers. This needs to be taken into consideration when expressing the risks of screening to participants.

The overall risk-stratified screening approach must also be deemed acceptable to the public. A community jury study explored the social and ethical considerations associated with risk-stratified screening [45]. The study showed that members of the public view risk-stratification as a positive way to enable screening programmes to: identify individuals at risk, reduce false positive results, increase the efficiency of screening, enable improved resource allocation and increase awareness of cancer risk. However, a key public concern was the perceived fairness and equity of the screening programme (Table 3). Studies exploring risk-stratified cancer screening in general, as well as work specific to kidney cancer, consistently highlight that certain approaches are considered more acceptable than others. In a population-based survey (N=668), participants were offered a series of hypothetical

scenarios in which risk-stratified screening for kidney cancer was implemented based on: age alone, sex alone, age and sex combined, a simple risk score (age, sex, body mass index, smoking status), a complex risk score additionally incorporating family history and lifestyle, or a genetic risk score [46]. Generally, risk-stratified screening was considered acceptable, and participants stated they would be more likely to attend screening if they were identified as being high-risk. This suggests risk-stratification may lead to higher rates of screening uptake. However, only 59% of participants found screening based on sex alone to be acceptable, compared to other strategies: acceptability was 83% for age alone, the more comprehensive risk score or a genetic risk score, 74% for the simple risk score and 65% for age and sex [46]. Screening based on sex alone was found to be the least acceptable option compared to other risk-stratification screening approaches [46], suggesting there may be concerns regarding fairness. This has important implications for kidney cancer screening, given the disease is more common in men and previous modelling studies suggest that screening may be cost-effective in men but not women[14], and that offering screening to men alone may be more efficient that offering screening to both sexes [24]. Additionally, this has important implications for aortic aneurysm screening, which is currently being offered only to men in the UK, as screening for women is deemed not cost-effective. Similarly, a discrete choice experiment of over 1000 participants [44] found that comprehensive scores based on genetic factors were considered preferable to scores based on lifestyle factors due to the higher relative importance given to non-modifiable versus modifiable factors by the participants. Identification of public preferences and barriers to screening attendance is key to enable a well-attended, implementable programme.

Harms associated with risk-stratified kidney cancer screening

Harms associated with risk-stratified screening can be classified into general harms (i.e. those which are common to population screening) and harms associated specifically with risk-stratification. Generally, harms of screening for kidney cancer include: the risk of false positives and false negatives, the identification of small renal masses of unclear diagnostic and prognostic significance which are associated with an increased likelihood of over-diagnosis and over-treatment, and the potential for negative impacts on quality of life. Small renal masses (SRMs, defined as <4cm in diameter) represent a unique challenge as a proportion of these have uncertain clinical potential at diagnosis. It is not always possible to pre-operatively accurately differentiate benign from malignant SRMs using contrast-enhanced CT, the gold standard imaging investigation [47,48], meaning a proportion of patients may have kidney surgery for a mass which may be diagnosed as benign on post-operative histopathology. Increased use of pre-operative MRI and/or renal biopsy as well as advances in the characterisation of SRMs using detailed patient registries [49] aims to tackle this challenge [10]. Further research is being undertaken evaluating biomarkers as well as novel imaging approaches (including the use of contrast enhanced ultrasound, and artificial intelligence algorithms to aid reporting of CTs) to improve the differentiation of SRMs at diagnosis [47]. Additionally, although some SRMs may demonstrate rapid growth, two thirds of SRMs may remain stable in size or grow slowly [10]. Increased use of minimally invasive approaches to treat SRMs (such as ablation) or even surveillance, aims to limit over-treatment[8]. Furthermore, it remains unclear if screening for kidney cancer will lead to increased detection and a stage shift and survival benefit compared with the standard of care, or whether screening is simply associated with increased detection (and would

primarily increase the number of low risk SRMs detected), given no studies have been undertaken to explore this. Lastly, while screening tests may lead to the identification of incidental findings, although some of these may be beneficial (such as the identification of aneurysms or other abdominal cancers when screening for kidney cancer using abdominal CT), others may lead to harms such as uncertainty, patient worry and increased investigations. These are important challenges that must be addressed when exploring a screening programme for kidney cancer.

One of the unique challenges associated with risk-stratified screening is that (depending on the exact criteria used to select people to invite) the majority of kidney cancer cases may occur in people who are deemed low risk and, therefore, are not invited to screening. Indeed, as described above, it has been estimated that risk-stratified screening using the best available risk models may detect approximately 22-33% of kidney cancer cases, meaning the majority of cancers are missed. This needs to be communicated effectively to the individuals being screened, as missed cancers could erode public trust in the screening programme and negatively affect attendance if the test is perceived to be inaccurate[16]. Additionally, there is a risk that individuals who have been told they are at low risk may ignore symptoms of kidney cancer and this could delay diagnosis.

Summary and conclusion

This narrative review represents a summary of the existing evidence on risk-stratified screening for kidney cancer. Different risk stratification approaches show promise including risk prediction models based on phenotypic data, which may enable early detection of kidney cancer alone, or in combination with other cancers via novel urine biomarkers. However, further work is required in this area, in particular, both genetic and biomarker risk assessment are not yet ready for application to screening programmes. Potential harms of risk-stratified screening have been identified and some potential mitigations have been suggested. Further, while the public acceptability of both kidney cancer screening and risk-stratified screening has been established prospectively, the results of the YKST study will be crucial in determining the acceptability and feasibility of combined screening for kidney and lung cancers in practice.

Table 1: Potential screening tools for kidney cancer early detection (reproduced with permission from [50])

Tool	Advantages	Disadvantages
Ultrasound	- Non-invasive - Well tolerated. - Relatively inexpensive - Widely available - Does not involve ionizing radiation - Most well researched screening tool. A number of observational studies have been performed, however these collected only limited data, none were randomised, and all were published more than a decade ago [11] - Potential for combination with the existing ultrasound-based AAA screening program [31]. - Focused renal ultrasound has the advantage of imaging the kidney exclusively, therefore reducing the number of incidental findings in other abdominal organs. Conversely, imaging of the whole abdomen may identify other conditions, thus maximising benefit of screening.	- Operator dependent - Accuracy depends on lesion size: detection of 85-100% tumours >3cm in size, but only 67-82% of tumours 2-3cm in size, therefore there is a potential for false negatives [51,52]. - Dependent on anatomical factors such as obesity and presence of overlying bowel gas.
Low-dose non-contrast CT	- Most sensitive and specific of the proposed screening tools. - CT chest performed as part of lung cancer screening may be extended to include the kidneys. The Yorkshire Kidney Cancer Screening Trial, currently underway, is investigating the feasibility of this approach.	- Ionizing radiation - High cost and significant number of incidental findings suggest abdominal CT or whole-body CT for the simultaneous detection of a number of conditions is unlikely to be cost-effective [53-55].
Urinary dipstick	- Non-invasive, quick, cheap - Can be performed in primary care with minimal training or at home by the patient themselves. - Can be used to screen for urological malignancies in combination. - In patients with non-visible haematuria, cancer detection rates are: 0%-16% for bladder cancer, 0%-3.5% for upper tract urothelial cancer and 0%-9.7% for kidney cancer [56].	- Non-visible haematuria is a very common and non-specific finding, meaning screening using dipstick would generate a high volume of participants requiring further investigation, to detect only a very small number of RCCs [10]. - High number of false negatives as only 35% of individuals with kidney cancer have visible or non-visible haematuria, compared to 94% in patients with urothelial carcinoma [57]. - A feasibility study of population screening utilising home urinary dipstick in 1,747 men aged 50 to 75 years demonstrated that the prevalence of non-visible haematuria

		was 23%. However, only one kidney cancer was detected and one kidney cancer was missed [58].
Plasma and urinary biomarkers	- Non-invasive - Perhaps the most promising biomarkers are: urinary Aquaporin-1 and perilipin-2 [59] and plasma KIM-1[60]	- A number of plasma and urinary biomarkers have been investigated including proteins [61], urinary exosomes and circulating tumour DNA (ctDNA). None have been adopted into clinical practice yet, however ctDNA remains the most promising tool [36].

Table 2: Modifiable and non-modifiable risk factors for kidney cancer that may be used in a risk-prediction model (adapted from [16])

Risk factor	Relative risks (RRs) and comments
Modifiable factors	
Smoking	• RR = 1.31 (95% CI: 1.22–1.40) for smokers versus non-smokers [62]
Obesity	• RR = 1.77 (95% CI: 1.68–1.87) for obesity (BMI ≥30) versus a normal BMI [63]
Hypertension	• RR = 1.70 (95% CI: 1.30–2.22) for patients with hypertension versus those without hypertension [64] • Meta-analysis reported 67% increased risk in patients with hypertension [65]
Diabetes	• Diabetes is associated with increased risk of kidney cancer, however it is difficult to ascertain if this is an independent link or whether this is due to potential confounders (smoking, obesity, and hypertension) [66,67]
Non-modifiable factors	
Age	• Kidney cancer incidence increases with age [68] • Global crude incidence, per 100,000 = 4.3 in 40–49 years, 10.8 in 50–59 years, 20.3 in 60–69 years, and 29.6 in 70–79 years [69]
Sex	• Kidney cancer incidence shows 2:1 male predominance across the world [69] • May be related to various confounders including modifiable risk factors of kidney cancer (smoking, obesity, or hypertension) as well as intrinsic biological variances
Race	• Racial disparities between black and Caucasian have been highlighted • ASRs of kidney cancer incidence in black versus white individuals, per 100,000 = 16.4 versus 13.5 in males and 8.1 versus 7.0 in females [70]
Family history	• RR = 2.2-fold when patients have kidney cancer history in any degree relatives [71] • RR = 4.3-fold when patients have kidney cancer history in first-degree relatives [71]

Abbreviations: ASR = age-standardised rate; BMI: body mass index; CI: confidence interval; RR= relative risk

Table 3: Public concerns regarding risk-stratified screening[45]

	Public concerns
-	Some individuals may be "missed" from screening invitations. For example, risk stratification based on GP health records may miss individuals not registered with a GP or those with incomplete health records.
-	Some "low risk" individuals may be missed from screening and may develop cancer. In particular, the public was concerned regarding missing cancers in younger individuals.
-	Concerns about the accuracy of measuring certain risk factors that may either change through time (for example, smoking status and BMI may fluctuate) or may be self-reported. In particular, there were concerns that individuals may exaggerate or even lie about their risk factors to access screening, giving them an unfair opportunity to claim NHS resources. Conversely, individuals may lie and "down-play" these same self-reported risk factors (e.g. smoking status and BMI) as they may be embarrassed about their behaviour and may want to avoid social stigma.
-	Using modifiable risk factors, such as BMI and smoking status, may raise concerns regarding fairness as it may be viewed as "favouring people who deliberately made unhealthy choices" and that it is "unjust or unfair for people who strive to be healthy not to be offered [screening]."
-	A key concern regarding the use of certain non-modifiable risk factors (such as sex, race and socio-economic status) that may lead to inadvertent discrimination; for example, it may not be fair to prioritise health resources to one sex and not the other.
-	Concerns that risk stratified screening may lead to an increase burden on the health service beyond age-based population-level screening, due to the added strain of assessing risk.
-	Using genetic markers risks reinforcing genetic determinism

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