2022 WUOF/SIU International Consultation on Urological Diseases: Kidney Cancer Screening and Epidemiology

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Abstract

The incidence of renal cell carcinoma (RCC) has risen worldwide over the past few decades, and this has been associated with a stage shift. Survival outcomes of RCC depend largely on the stage at diagnosis. Although overall mortality has stabilized or declined in most countries, survival remains poor in late-stage disease, suggesting early detection may improve overall survival outcomes. A number of potential candidate screening tools have been considered (including urinary dipstick, blood- and urine-based biomarkers, ultrasound, and computed tomography [CT]), though it may be that a combination of these approaches may be optimal. Ultimately, the sensitivity and specificity of the chosen screening tool will determine the rate of false positives and false negatives, which must be minimized. One of the key challenges is the relatively low prevalence of the disease, which might be overcome by performing risk-stratified screening or screening for more than one condition (such as combined lung and kidney cancer screening). Both approaches have been shown to be acceptable to the general public, and they may maximize the efficiency of screening while reducing harms. Indeed, quantifying benefits and harms of screening is key (including the impact on overdiagnosis and quality of life). Whether screening for RCC will lead to a stage shift and the impact on survival are the decisive missing pieces of information that will determine whether the screening program might be adopted into clinical practice (along with feasibility, acceptability, and cost-effectiveness).

Epidemiology and Risk Factors for RCC

Incidence and Risk Factors

Renal cell carcinoma (RCC) RCC is the 9th most frequently diagnosed cancer in men and the 14th most common in women globally, accounting for 2.2% of all new cancer diagnoses (Table 1)[1]. The incidence of RCC demonstrates geographic variability (Figure 1)[2,3]. The International Agency for Research on Cancer (IARC), established in 1965 by the World Health Assembly, provides comprehensive information on global cancer epidemiology by aggregating data from 343 population-based cancer registries in 65 countries[4]. The registry data is currently available online at the Global Cancer Observatory as the GLOBOCAN database[2]. According to the GLOBOCAN 2020 report, the age-standardized incidence of kidney cancer is highest in Northern America, followed by Europe, Oceania, Latin America and the Caribbean, Asia, and Africa (Figure 1). The incidence of RCC has generally increased over time in both sexes, and is predicted to continue to rise over the next 15 years, although there is some variability across countries[2,3].

Key Words

Renal cell carcinoma, stage shift, RCC screening tools, risk-stratified screening

Competing Interests

None declared.

Article Information

Abbreviations

AAA abdominal aortic aneurysm

ASR age-standardized rate

AUC area under the curve

BMI body mass index

ccRCC clear cell renal cell carcinoma

chRCC chromophobe renal cell carcinoma

CT computed tomography

ctDNA circulating tumor DNA

KIM-1 kidney injury molecule-1

NV nonvisible

RCC renal cell carcinoma

RCT randomized controlled trial

SRMs small renal masses

The geographic distribution and rising incidence of RCC have been partially attributed to variation in risk factors for the disease as well as differences in healthcare delivery systems, as detailed below[5–7].

A number of modifiable and nonmodifiable risk factors for RCC have been identified (**Table 2**). The aging population and rising prevalence of certain risk factors (such as obesity, hypertension, and diabetes) contribute to increasing rates of the disease[5–7]. In addition, increased incidental detection reflects the widespread use of abdominal imaging. For example, in the United States, it is estimated that 43% of individuals aged 65–85 years on Medicare undergo either thoracic or abdominal computed tomography (CT) in a 5-year period, and for every 1000 CT scans performed there are 4 additional nephrectomies[8]. Additionally, 2 studies have shown a statistically significant increase in the number of renal cancers detected among newly insured patients secondary to widening access to care through expansion of healthcare insurance[9,10].

Incidental detection has also contributed to a stage shift (i.e., detection of disease at an earlier stage), which was noted until the mid-2000s and has subsequently stabilized[11–13]. Clinical stage I tumors accounted for 43% of all kidney cancers diagnosed in 1993; the percentage increased to 57% in 2004[11] and leveled off around 70% after 2007, although the size of localized tumors continued to decline[12]. Overall, between 1993 and 2004, 50.6%, 26.7%, and 22.7% of kidney cancer patients were diagnosed with stage I, stage II or III, and stage IV, respectively[11]. In contrast, between 2004 and 2015, 70.3%, 10.5%, 8.3%, and 11.0% of patients were diagnosed with stage I (including 47.5% stage Ia and 22.8% stage Ib), stage II, stage III, and stage IV, respectively, highlighting a significant increase of stage I as well as a decrease of stage IV RCC[12].

Mortality

The crude mortality rate of kidney cancer was 13th in men and 14th in women (**Table 1**; **Figure 2**)[1]. Europe has the highest age-standardized mortality rate, followed by Northern America/Oceania, Latin America and the Caribbean, Asia, and Africa (**Figure 2**). The age-standardized rate and the cumulative risk for kidney cancer death have been stabilizing in many countries, and have declined particularly in Europe and Northern America during the past one to 2 decades in both sexes[2,14]. Survival outcomes of RCC depend largely on the stage at diagnosis. The most recent report based on the National Cancer Database in the United States showed that the 5-year survival rate was 93%, 70%, and 13% in patients with localized, regional, and distant RCC, respectively[15]. In this report, the mortality data were collected by the National Center for Health Statistics[15]. Similar survival outcomes were also observed in the United Kingdom; 5-year survival was 87% in stage I compared to 12% in stage IV RCC[16]. The decline in kidney cancer mortality may, therefore, be related to earlier diagnosis, as well as improved treatment strategies and recent advances in systemic therapy[12,17].

Population Screening
Rationale for Screening

The relatively large proportion of patients with RCC who are diagnosed at a late, advanced, or metastatic stage due to the absence of symptoms and the poor survival in this group are the main drivers for the need to improve the early detection of RCC. Initiatives to raise public awareness of hematuria have not been successful in improving detection of RCC[18], suggesting that a more systematic identification approach may be necessary. Screening for RCC has the potential to improve survival outcomes by enabling earlier diagnosis and treatment[19,20]. No randomized controlled trials (RCTs) of screening for RCC have been performed and due to insufficient evidence, international urology and oncology associations have yet to publish guidelines on this topic[21–27]. Screening and early detection of RCC have been identified as a key research priority in 3 independent priority-setting initiatives[28–31], and patient groups have been vocal in their desire to champion this agenda[32]. The "sojourn time," also known as the "preclinical period," refers to the length of time during which an individual with RCC has not yet received a diagnosis, and would therefore benefit from early detection via screening. Cancers with very short or very long sojourn times are not ideal screening candidates. Imaging studies have suggested the sojourn time for RCC is between 3.7 and 5.8 years[33]. Scelo et al. demonstrated raised kidney injury molecule-1 (KIM-1) plasma levels up to 5 years prior to RCC

TABLE 1.

Age-standardized rate and cumulative risk of kidney cancer incidence and mortality (GLOBOCAN 2020 report)[1]

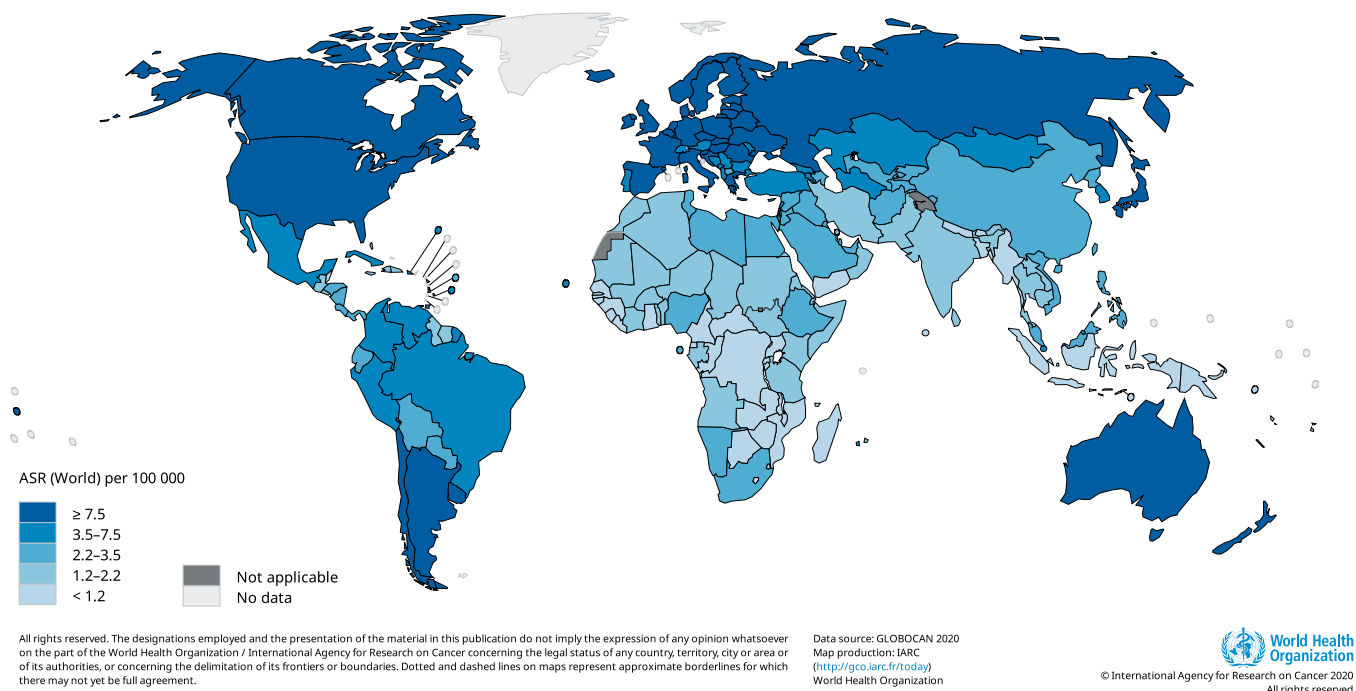|	Incidence		Mortality	
	ASR, per 100 000[a]	Cumulative risk, %[b]	ASR, per 100 000[a]	Cumulative risk, %[b]
Worldwide				
Male	6.1	1.45	2.5	0.81
Female	3.2	0.76	1.2	0.39
Both sexes	4.6	1.06	1.8	0.57
Europe				
Male	13.1	2.78	4.5	1.41
Female	6.4	1.36	1.7	0.58
Both sexes	9.5	1.96	2.9	0.91
Northern America				
Male	16.1	3.23	3.0	0.95
Female	8.6	1.69	1.3	0.45
Both sexes	12.2	2.39	2.1	0.67
Latin America and the Caribbean				
Male	6.3	1.37	2.8	0.79
Female	3.3	0.74	1.3	0.37
Both sexes	4.7	1.02	2.0	0.55
Oceania				
Male	12.4	2.83	3.0	1.05
Female	5.4	1.27	1.3	0.51
Both sexes	8.8	2.00	2.1	0.75
Asia				
Male	3.8	0.89	2.0	0.61
Female	1.9	0.45	0.90	0.30
Both sexes	2.8	0.65	1.4	0.44
Africa				
Male	2.1	0.48	1.4	0.43
Female	1.5	0.24	0.98	0.21
Both sexes	1.8	0.34	1.2	0.30

ASR: age-standardized rate.
[a]The age-standardized rate (ASR) was adjusted to the world standard population.
[b]The cumulative risk was the probability of kidney cancer development or death in a lifetime defined as 0–74 years.
Source: Reprinted from GLOBOCAN 2020 report, Global Cancer Observatory, Cancer Today. Ferlay J, Ervik M, Lam F, et al., eds. Age-standardized rate and cumulative risk of kidney cancer incidence and mortality. World Health Organization, International Agency for Research on Cancer, Copyright 2022[1].
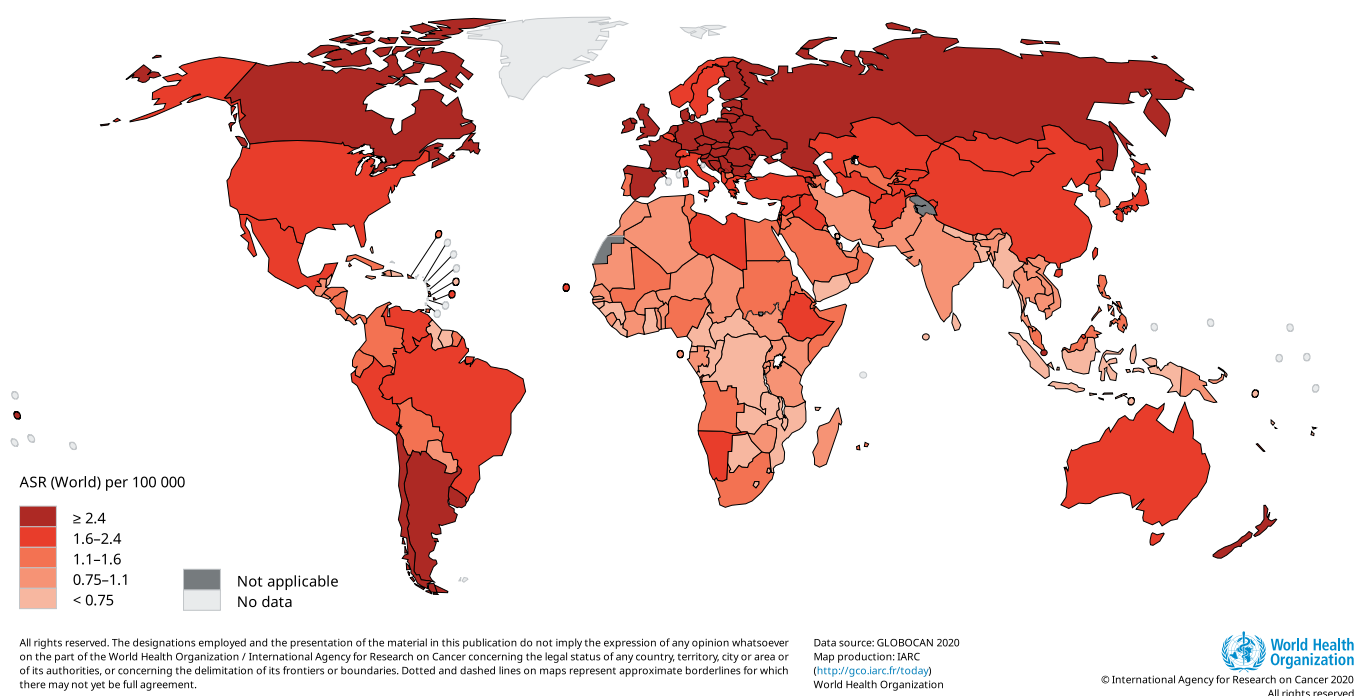
FIGURE 1.

Age-standardized rate of kidney cancer incidence

ASR (World) per 100 000

- ≥ 7.5
- 3.5–7.5
- 2.2–3.5
- 1.2–2.2
- < 1.2
- Not applicable
- No data

Data source: GLOBOCAN 2020
Map production: IARC
(http://gco.iarc.fr/today)
World Health Organization

World Health Organization

Source: Reprinted from GLOBOCAN 2020 report, Global Cancer Observatory, Cancer Today. Ferlay J, Ervik M, Lam F, et al., eds. Age-standardized rate of kidney cancer incidence. World Health Organization, International Agency for Research on Cancer, Copyright 2022[1].

FIGURE 2.

Age-standardized rate of kidney cancer mortality

ASR (World) per 100 000

- ≥ 2.4
- 1.6–2.4
- 1.1–1.6
- 0.75–1.1
- < 0.75
- Not applicable
- No data

Data source: GLOBOCAN 2020
Map production: IARC
(http://gco.iarc.fr/today)
World Health Organization

World Health Organization

Source: Reprinted from GLOBOCAN 2020 report, Global Cancer Observatory, Cancer Today. Ferlay J, Ervik M, Lam F, et al., eds. Age-standardized rate of kidney cancer incidence. World Health Organization, International Agency for Research on Cancer, Copyright 2022[1].

TABLE 2.

Modifiable and nonmodifiable risk factors for RCC

Risk factor	Relative risks (RRs) and comments
Modifiable factors	
Smoking	Established risk factor for RCC[34–37] RR 1.31 (95% CI, 1.22–1.40) for smokers versus nonsmokers[34]
Obesity	Established risk factor for RCC[35,37–39] RR 1.77 (95% CI, 1.68–1.87) for obesity (BMI ≥ 30) versus a normal BMI[39]
Hypertension	Established risk factor for RCC[37] RR 1.70 (95% CI, 1.30–2.22) for patients with hypertension vs. those without hypertension[37] Meta-analysis reported 67% increased risk in patients with hypertension[40]
Diabetes	Controversial whether diabetes is an independent risk factor for RCC due to potential confounders (smoking, obesity, and hypertension)[7,41]
Diet	Meat: potential risk factor for RCC; may be partially related to the carcinogens formed in the cooking process[42,43] Fruit and vegetables: may be protective (particularly for cruciferous vegetables)[44,45] Alcohol: may be protective; an inverse relationship between moderate alcohol intake (< 60 g/day) and RCC risk is reported[46,47]
Occupation	Trichloroethylene: may modestly increase the risks of several cancers including RCC[48–50]. Toxicity is officially acknowledged by the Environmental Protection Agency in the United States
Drug exposure	Acetaminophen and NSAIDs other than aspirin: significantly associated with an increased incidence of kidney cancer[51] Aspirin: No increase in RCC incidence[51]
Nonmodifiable factors	
Age	RCC incidence increases with age[14] 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[1]
Sex	RCC incidence shows 2:1 male predominance across the world[1] (Table 1) May be related to various confounders including modifiable risk factors of RCC (smoking, obesity, or hypertension) as well as intrinsic biological variances
Race	Racial disparities between black and Caucasian has been highlighted ASRs of kidney cancer incidence in black vs. white individuals, per 100 000 = 16.4 vs. 13.5 in males and 8.1 vs. 7.0 in females[2] ASRs of kidney cancer incidence in black vs. white individuals, per 100 000 = 16.4 vs. 13.5 in males and 8.1 vs. 7.0 in females[2]
Family history	RR 2.2-fold when patients have RCC history in any-degree relatives[52] RR 4.3-fold when patients have RCC history in first-degree relatives[52]

ASR: age-standardized rate; BMI: body mass index; CI: confidence interval; NSAID: nonsteroidal anti-inflammatory drug; RCC: renal cell carcinoma.

diagnosis[53], which is in keeping with the estimated sojourn time. Taken together, these studies suggest that there is a length of time during which asymptomatic patients might benefit from screening interventions. Any screening program for RCC, however, must be evaluated with the Wilson and Jungner criteria in mind[54], to minimize risks to the general population while maximizing benefits for individuals. The Wilson and Jungner criteria serve as guiding principles and a framework to evaluate potential screening programs and assess their utility and feasibility within the existing health service[54].

Screening Modality

A successful screening strategy relies on a screening tool that is accurate, reliable, acceptable to the public, and scalable (i.e., can be rolled out on a population level by the existing health service). A number of screening approaches have been considered, each with advantages and disadvantages, although the ideal screening tool has yet to be identified.

Urinary Tests

Urinary tests represent an ideal tool due to their noninvasive nature, ease of collection and storage, and acceptability by the general public[55]. This strategy could involve either a point-of-care test (such as dipstick for hematuria) or laboratory test (urinary biomarkers). Dipstick tests are cheap, readily available, and require minimal training; however, color changes may be open to subjective interpretation. Nonvisible (NV) hematuria is defined as blood in the urine detected by urinary dipstick or microscopy, which is not visible to the naked eye (as opposed to visible hematuria, which is macroscopic)[63]. The main concerns are the nonspecific nature of NV hematuria for RCC, the high number of incidental findings, and the unacceptably high rate of false positives and false negatives[20,64]. Therefore, screening for RCC based around dipstick-detected NV hematuria is not currently recommended (though there may be benefits for bladder cancer detection)[65]. The vast majority of patients diagnosed with RCC will not have hematuria, meaning there would be a large number of false negatives. The prevalence of hematuria in RCC is 35% (prevalence 17.5% visible and 17.5% nonvisible hematuria), compared to 94% in bladder and ureter urothelial cancers[66]. The prevalence of NV hematuria may be as high as 20% to 30% in the general population[64,67]; however, < 1% of individuals with NV hematuria are found to have RCC and 5% are found to have bladder cancer[63]. Conversely, urinary dipstick may identify a large number of nonmalignant urological diseases that are associated with NV hematuria (including renal stones, cysts, etc.) as well as medical diseases associated with proteinuria or glycosuria (renal disease, diabetes, infection, etc). The high volume of individuals requiring further investigation and the high number of incidental findings preclude this as a cost-effective screening strategy for RCC.

Urinary biomarkers would represent the ideal screening tool; however, to date none are validated or approved for use in clinical practice[68]. A number of different analytes have been considered, including urinary proteins, cell-free tumor DNA, microRNAs, and exosomes. Perhaps the most well-studied group is urinary proteins, including aquaporin-1, perilipin-2, carbonic anhydrase-9, Raf-kinase inhibitory protein, nuclear matrix protein-22, 14–3–3 Protein β/α, and neutrophil gelatinase-associated lipocalin[68]. Aquaporin-1 and perilipin-2 have been evaluated in a prospective study of 720 patients undergoing screening CT, 80 healthy controls, and 19 patients with RCC. In this cohort, these 2 biomarkers used in combination achieved an area under the curve (AUC) of > 0.99 for RCC[69]. Although these 2 proteins may be good markers for clear cell renal cell carcinoma (ccRCC) and papillary renal cell carcinoma (pRCC), levels are low or negative in chromophobe renal cell carcinoma (chRCC), meaning that screening would miss these cancers[19]. Further prospective validation in an independent cohort is warranted.

Blood Tests

Blood-based tests represent another potentially useful option due their relative public acceptability and presumed relatively low cost. Analytes similar to those identified in urine may be used, such as proteins, circulating tumor DNA (ctDNA), microRNAs, and exosomes. KIM-1 is a glycoprotein that reflects injury to the proximal convoluted tubule of the kidney (from which ccRCC and pRCC are derived). KIM-1 blood levels may be elevated 5 years prior to a diagnosis of RCC[53]. One of the main disadvantages is the low specificity of KIM-1 (levels may be elevated in kidney injury). Furthermore, KIM-1 levels are not elevated in patients with renal tumors derived from the distal nephron (e.g., chRCC and collecting duct RCC), limiting applicability as a screening tool. Cancer screening using ctDNA has recently received significant media attention and has entered large-scale validation studies[70–72]. A number of studies have been published evaluating ctDNA for the simultaneous detection of multiple cancer subtypes with the aim of pan-cancer screening[70,73–75]. Although initial reports evaluating mutations[76] and methylation patterns[74] in ctDNA suggested that patients with RCC may have lower levels of ctDNA than those with other malignancies, more recent reports evaluating DNA methylation appear more promising[77]. Nuzzo et al.[77] evaluated ctDNA methylation using cell-free methylated DNA immunoprecipitation and high-throughput sequencing (cfMeDIP–seq) in a case-control study. The

study cohort included 99 ctDNA samples from patients with RCC (of which 33% were from patients with stage I–II disease), 21 samples from patients with stage IV bladder cancer, and 28 healthy controls. The overall AUC for the detection of RCC was 0.99, suggesting ctDNA may be detected in patients with RCC across the spectrum of disease severity, raising the possibility that in future this could potentially be used to enable earlier disease detection.

Unfortunately, thus far, neither urine- nor blood-based biomarkers have achieved sufficient sensitivity and specificity required for implementation in clinical practice. Further research on minimally invasive biomarkers as a screening tool, in prospective cohorts, is warranted.

Ultrasound

Ultrasound is perhaps the most well-studied screening method for RCC, with a number of observational studies published in the 1990s and early 2000s[78–85]. The main drawback is that accuracy is dependent on operator experience, anatomical factors (including obesity and overlying bowel gas), and lesion size. There is a potential for false negatives, as ultrasound can detect 85% to 100% tumors > 3 cm in size, but only 67% to 82% of tumors of 2–3 cm in size[86,87]. Advantages of ultrasound include the relative acceptability by the general public, as it is pain-free and noninvasive (compared to blood tests). Ultrasound is widely available, does not involve ionizing radiation, and is relatively inexpensive compared to CT. Furthermore, focused renal ultrasound may be performed, imaging the kidneys alone rather than the entire abdomen, therefore reducing the time and cost of the scan and avoiding incidental detection of indeterminate lesions in other abdominal organs, which may require additional investigation with associated costs. Another potential advantage is the opportunity to combine screening for renal cancer with the existing abdominal aortic aneurysm (AAA) screening program, currently underway in a number of countries[88–90]. A combined approach would reduce the overall cost of the screening intervention and maximize cost-effectiveness, although currently AAA is only recommended for men and not women. To the best of our knowledge, Malaeb et al.[85] is the first and only study to explore the combined screening of RCC and AAA, demonstrating this is a feasible approach that is well tolerated by patients. Although this study is promising, none of the ultrasound studies were randomized in nature, meaning the impact of the intervention on survival remains unknown.

Computed Tomography

Use of CT has increased in recent decades due to technological advances (enabling increased resolution, reduced scanning times, and lower radiation dose), increasing availability and reducing costs[8,91].

Contrast-enhanced CT is the gold-standard diagnostic imaging technique to evaluate small renal masses in patients with suspected RCC (e.g., if a mass is identified on ultrasound or there is visible hematuria). Contrast uptake can enable the differentiation between benign and malignant disease, and visualization of tumor and vessel anatomy that can guide operative management approaches. However, the utility of contrast-enhanced CT as a screening tool in the general population is limited by the use of contrast (which may be nephrotoxic), the relatively high radiation dose, and cost, particularly given the low prevalence of RCC. However, low-dose unenhanced CT has the advantage of providing less radiation dose and no contrast.

Whole-body CT has been proposed as a potential screening tool for the combined detection of multiple malignant and nonmalignant diseases (e.g., abdominal cancers, AAA, etc.). Although a number of studies have been performed, the main drawback of performing whole-body scans is the high number of incidental findings, false positives, and findings of unknown clinical potential. For example, Millor et al.[92] reviewed 6516 whole-body screening CTs (which included unenhanced chest CT, enhanced abdominal CT, cardiovascular, and bone assessments). Fewer than 2% of individuals had normal scans, meaning that > 98% had to undergo further investigations with significant costs, burden to the health service, and anxiety for the individual. Only 1.5% of individuals were found to have a malignancy (35 of 96 were RCC). As a result, whole-body CT to screen for kidney cancer as a standalone test in an unselected population is unlikely to be a cost-effective strategy at present[93], though in future automated interpretation of imaging features using machine learning may increase the accuracy and feasibility of this strategy[95]. An alternative approach is to add low-dose noncontrast abdominal CT scans to the low-dose unenhanced chest CT scans currently being investigated for lung cancer screening. The Yorkshire Kidney Screening Trial (NCT05005195), currently underway, is a novel study and the first to evaluate the added benefit of screening for RCC by extending the low-dose chest CT to image the kidneys in 55–80-year-old smokers and ex-smokers undergoing lung cancer screening enrolled in the Yorkshire Lung Screening Trial[95]. It is postulated that combined lung and kidney cancer screening may maximize cancer detection rates while reducing costs.

Screening Population

The ideal population to whom screening for RCC should be offered is unknown. Meta-analyses have estimated that screening 1000 individuals using ultrasound would identify between 1 and 2 patients with RCC[78], while using CT would identify between 1 and 3 (the pooled

prevalence of RCC is 0.17% (95% CI 0.09–0.27%) and 0.21% (95% CI, 0.14–0.28%) in ultrasound and CT respectively)[33,78]. One of the main challenges is the relatively low prevalence of RCC. Indeed, a health economic analysis of screening for RCC using ultrasound identified prevalence of RCC as the greatest determinant of cost-effectiveness[96].

Risk-stratified screening may enable more efficient identification of RCC, focusing on high-risk individuals and therefore maximizing benefits while reducing costs and harms for those at low risk. A systematic review of risk-prediction models for RCC[97] identified 11 models that report performance measures and could potentially be used. Fewer than 20% (2 of 11) had been validated in an external population, highlighting one of the limitations of current models. The most commonly included factors were sex, age, smoking status, body mass index (BMI), and hypertension, which is consistent with the known data on risk factors for RCC. However, none of these risk factors are specific for RCC. Only one study considered genetic risk (i.e., single-nucleotide polymorphisms) and biomarker studies were characterized by a high risk of bias. The models identified in the systematic review were externally validated in > 450 000 participants within the UK Biobank cohort[98]. Five models had reasonable calibration and discrimination, with an area under the receiver operating characteristic curve between 0.61 and 0.72. All the models performed less well in women, compared to men. Additionally, although the models were better at identifying individuals at high risk for RCC than age and sex alone, the improvement was small. Risk-prediction models for RCC based on genetic factors performed poorly compared to the best genetic risk models for other cancers, suggesting more research on this topic is needed[99]. Future incorporation of biomarkers into risk scores could improve performance.

Screening Implementation and Public Acceptability

If screening is demonstrated to improve disease-specific survival, it is crucial to consider implementation within the existing healthcare delivery system. The cost of screening is not limited to the intervention itself, but includes the associated costs of investigating incidental findings and the cost of treatment of diagnosed conditions. The cost-effectiveness of any screening intervention needs to be demonstrated prior to the screening program being accepted into clinical practice. Other important considerations are in regard to program delivery, including optimal screening location (e.g., primary care, secondary care, screening vans in public spaces), training an adequate workforce to deliver

screening (e.g., ultrasound delivered by technicians vs. sonographers), and quality control (e.g., audit for laboratories undertaking biomarker work or facilities offering imaging).

Public acceptability of the program will also be key to ensure high attendance rates. A survey has shown that members of the general public would be "very likely" or "likely" to undergo each of the following screening tests: urine test, 94%; blood test, 90%; ultrasound, 90%; low-dose CT, 79%; and low-dose CT offered as part of lung screening, 95%[55]. In addition, 83% reported that tailoring the starting age of RCC screening based on a risk score incorporating phenotypic or genetic risk was acceptable, and 85% reported they would be more likely to attend screening if the risk score suggested they were high risk[100]. The high anticipated intention to attend screening and positive attitudes toward risk-stratified screening are promising.

Unknown Benefits and Harms

Although screening could have many potential benefits, there are still many unknowns that require further research (Table 3). Importantly, it is unclear whether screening would lead to increased RCC diagnoses (including a stage shift) in view of the high rates of incidental detection. Crucially, it is unknown whether screening leads to a survival benefit. Another main challenge relates to increased detection of small renal masses (SRMs, defined as < 4 cm in diameter), which are difficult to characterize and therefore may lead to false positives or overdiagnosis of indolent lesions (Table 4). Ultimately, being able to clearly determine which SRMs require further investigation or treatment and developing pathways for the management of patients with SRMs based on competing risks are essential before any RCC population-based screening program can be implemented.

As screening is offered to a large number of asymptomatic individuals in order to detect only a small number of cancers, it is crucial to understand any quality of life (QoL) detriment associated with screening itself. None of the observational studies evaluating ultrasound screening for RCC assessed the impact on QoL[19]. There are a number of ways in which screening can cause harm (Table 4)[101–103]. These include physical harm, resulting from both the screening test and/or follow-up procedures; psychological harm, including increases in anxiety; treatment burden, including from subsequent invasive procedures and overdiagnosis; financial costs associated with travel and time off work to attend appointments and potential loss of earnings; social harm, resulting from social stigma or missing out on other activities; and dissatisfaction with health care.

Future Directions

In summary, the incidence of RCC has risen worldwide over the past few decades, and this has been associated with a stage shift. Survival outcomes of RCC depend largely on the stage at diagnosis. Although overall mortality has stabilized or declined in most countries, survival remains poor in late-stage disease, meaning that early detection could improve overall survival outcomes. A number of potential candidate screening tools are currently being investigated, though it may be that a combination of these approaches may be optimal. Ultimately, the sensitivity and specificity of the chosen screening tool will determine the rate of false positives and false negatives, which must be minimized. One of the key challenges is the relatively low prevalence of the disease, which might be overcome by performing risk-stratified screening or screening for more than one condition (such as combined lung and kidney cancer screening). Both approaches have been shown to be acceptable to the general public, and they may maximize the efficiency of screening while reducing harms. Whether screening for RCC will lead to a stage shift and the impact on survival are the decisive missing pieces of information that will determine whether the screening program might be adopted into clinical practice (along with feasibility, acceptability, and cost-effectiveness).

TABLE 3.

Research questions that remain to be addressed

Unknowns	Comments, challenges, and future direction
The ideal screening modality is unknown.	• Ideally a two-step approach would be adopted (such as for colorectal cancer screening), where an initial noninvasive test (e.g., urinary test) would be followed by a second, more advanced test (e.g., imaging).
The ideal screening population is unknown.	• The main challenge is the low prevalence of RCC, meaning that a large number of healthy individuals would have to be screened to identify only a small number of cases. • Risk-prediction models may identify individuals at high risk, therefore maximizing cost-effectiveness. However, existing models have a relatively low accuracy and are based on nonspecific risk factors.
Unknown whether screening for kidney cancer will translate into a survival benefit beyond length and lead time bias.	• No randomized controlled trials (RCTs) have been performed to date. • Ultimately, an RCT would be needed to demonstrate a survival benefit; however, due to the low prevalence of RCC, this would necessitate hundreds of thousands of participants with long-term follow-up, which is prohibitive.
Unknown whether screening will lead to increased detection and a stage shift (i.e., earlier detection) given high volume of abdominal imaging for other complaints and widespread incidental detection.	• It is estimated that 43% of individuals aged 65–85 years on Medicare in the United States undergo either a CT chest or CT abdomen over a 5-year period[8], meaning that it is unclear whether these individuals may benefit from further screening.
Unclear when to start screening and how often to screen.	• No premalignant lesion has been identified for RCC. • Thus far, studies have evaluated screening for RCC at a single time point rather than regular intervals[19].
Potential harms of screening and the impact on quality of life have not yet been fully quantified.	• See Table 4.
Unclear whether screening could be implemented in the current health service.	• Once the screening modality has been selected, further data will be needed on cost-effectiveness (based on a trial), feasibility, public acceptability, and potential uptake.

Adapted from Rossi SH, T. Klatte J, Usher-Smith J, Stewart GD. Epidemiology and screening for renal cancer. World J Urol.2018;36(9):1341–1353. doi:10.1007/s00345-018-2286-7, under the Creative Commons License.

TABLE 4.

Potential harms of screening for RCC
The following potential harms may depend on the screening modality that is ultimately chosen

Potential harms	Comment
False negatives	• False negatives are associated with real harms and anxiety to the individual. • May erode public trust in the screening program and negatively affect attendance if the test is perceived to be inaccurate.
False positives	• Unfortunately, it is not possible to accurately differentiate benign from malignant SRMs using contrast-enhanced CT, the gold standard imaging investigation[97,98]. • Renal biopsy is often under-utilised due to inadequate service provision, lack of expertise or low perceived clinical benefit. Biopsy is non-diagnostic in ~10% of cases[99] and it can be particularly difficult to distinguish oncocytoma from eosinophilic variants of chRCC and ccRCC. • A meta-analysis demonstrated approximately 25% of renal biopsies reported as oncocytoma are found to be malignant following excision[100]. Erring on the side of caution, patients with SRM are often offered surgery and as a result, approximately 20%-30% are found to have benign disease post-operatively, meaning they underwent unnecessary surgery, with associated morbidity and potential long-term effects on renal function[101,102].
Overdiagnosis and overtreatment of renal tumors that would not affect survival	• It is not possible to distinguish aggressive from indolent SRMs, meaning that screening could identify a large number of individuals with SRMs who would not benefit from treatment. • Increasing the use of active surveillance (which has been shown to be noninferior to primary intervention) especially in patients with comorbidities who may have a limited life expectancy, could reduce overtreatment[62]. • Recently, a growing number of observational studies are being performed that are increasing our understanding of the natural history of disease[62].
Incidental findings	• High cost of further investigations. • May have indeterminate clinical potential and result in increased patient anxiety. • However, imaging-based screening may identify additional conditions (such as other abdominal cancers or AAA) that could benefit patients.
Anxiety and worry	• Resulting from both the screening test and/or follow-up procedures.

*AAA: abdominal aortic aneurysm; ccRCC: clear cell renal cell carcinoma; chRCC; chromophobe renal cell carcinoma;
CT: computed tomography; SRMs: small renal masses.*

References

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, et al. Global Cancer Observatory, Cancer Today. International Agency for Research on Cancer.2020. Available at https://gco.iarc.fr/today. Accessed September 22, 2022.

2. Ervik M, Lam F, Laversanne M, Ferlay J, Bray F. Global Cancer Observatory, Cancer Over Time. *International Agency for Research on Cancer.*2020. Available at: https://gco.iarc.fr/overtime. Accessed September 22, 2022.

3. Smittenaar CR, Petersen KA, Stewart K, Moitt N. Cancer incidence and mortality projections in the UK until 2035. *Br J Cancer.*2016;115(9):1147-1155.

4. Bray F, Colombet M, Mery L, Piñeros M, Znaor A, Zanetti R, et al., eds. Cancer Incidence in Five Continents, Vol. XI. IARC Scientific Publication No. 166. Lyon: International Agency for Research on Cancer. Available from: https://publications.iarc.fr/597. Licence: CC BY-NC-ND 3.0 IGO.

5. Nguyen MM, Gill IS, Ellison LM. The evolving presentation of renal carcinoma in the United States: trends from the Surveillance, Epidemiology, and End Results program. *J Urol.*2006;176(6 Pt 1):2397-2400; discussion 400.

6. Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. *J Natl Cancer Inst.*2006;98(18):1331-1334.

7. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. *Nat Rev Urol.*2010;7(5):245-257.

8. Welch HG, Skinner JS, Schroeck FR, Zhou W, Black WC. Regional variation of computed tomographic imaging in the United States and the risk of nephrectomy. *JAMA Intern Med.* 2018 Feb 1;178(2):221-227. doi: 10.1001/jamainternmed.2017.7508.

9. Michel KF, Spaulding A, Jemal A, Yabroff KR, Lee DJ, Han X. Associations of Medicaid expansion with insurance coverage, stage at diagnosis, and treatment among patients with genitourinary malignant neoplasms. *JAMA Netw Open.*2021;4(5):e217051. doi: 10.1001/jamanetworkopen.2021.7051

10. Javier-DesLoges JF, Yuan J, Soliman S, Hakimi K, Meagher MF, Ghali F, et al. Evaluation of insurance coverage and cancer stage at diagnosis among low-income adults with renal cell carcinoma after passage of the Patient Protection and Affordable Care Act. *JAMA Netw Open.*2021;4(7):e2116267. Published online 2021 Jul 16. doi: 10.1001/jamanetworkopen.2021.16267

11. Kane CJ, Mallin K, Ritchey J, Cooperberg MR, Carroll PR. Renal cell cancer stage migration: analysis of the National Cancer Data Base. *Cancer.*2008;113(1):78-83. doi: 10.1002/cncr.23518.

12. Patel HD, Gupta M, Joice GA, Srivastava A, Alam R, Allaf ME, et al. Clinical stage migration and survival for renal cell carcinoma in the United States. *Eur Urol Oncol.*2019;2(4):343-348. doi: 10.1016/j.euo.2018.08.023.

13. Takagi T, Kondo T, Tanabe K. Stage migration of renal cell carcinoma at a single Japanese university hospital: 24-year study. *Int J Urol.*2014;21(4):429-430.

14. Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A, Bray F. International variations and trends in renal cell carcinoma incidence and mortality. *Eur Urol.*2015;67(3):519-530. doi: 10.1016/j.eururo.2014.10.002

15. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin.* 2021;71(1):7-33.

16. Cancer Research UK Kidney Cancer Statistics. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer. Accessed September 22, 2022.

17. Lalani AA, McGregor BA, Albiges L, Choueiri TK, Motzer R, Powles T, et al. Systemic treatment of metastatic clear cell renal cell carcinoma in 2018: current paradigms, use of immunotherapy, and future directions. *Eur Urol.*2019;75(1):100-110. doi: 10.1016/j.eururo.2018.10.010

18. Hughes-Hallett A, Browne D, Mensah E, Vale J, Mayer E. Assessing the impact of mass media public health campaigns. Be Clear on Cancer 'blood in pee': a case in point. *BJU Int.*2016;117(4):570-575. doi: 10.1111/bju.13205

19. Rossi SH, Klatte T, Usher-Smith J, Stewart GD. Epidemiology and screening for renal cancer. *World J Urol.* 2018;36(9):1341-1353.

20. Usher-Smith J, Simmons RK, Rossi SH, Stewart GD. Current evidence on screening for renal cancer. *Nat Rev Urol.*2020;17(11):637-642.

21. Guo J, Ma J, Sun Y, Qin S, Ye D, Zhou F, et al. Chinese guidelines on the management of renal cell carcinoma (2015 edition). *Chin Clin Oncol.*2016;5(1):12. doi: 10.3978/j.issn.2304-3865.2015.11.01

22. Ljungberg B, Albiges L, Abu-Ghanem Y, Bedke J, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2022 Update. *Eur Urol.*2022;82(4):399-410.

23. Campbell SC, Clark PE, Chang SS, Karam JA, Souter L, Uzzo RG. Renal mass and localized renal cancer: evaluation, management, and follow-up: AUA Guideline: Part I. *J Urol.* 2021;206(2):199-208. doi: 10.1097/JU.0000000000001911

24. Richard PO, Violette PD, Bhindi B, Breau RH, Kassouf W, Lavalle LT, et al. Canadian Urological Association guideline: Management of small renal masses - Summary of recommendations. *Can Urol Assoc J.*2022;16(2): E61–E75. doi: 10.5489/cuaj.7763

25. Kanesvaran R, Porta C, Wong A, Powles T, Ng QS, Schmidinger M, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with renal cell carcinoma. *ESMO Open.* 2021;6(6):100304. doi: 10.1016/j.esmoop.2021.100304

26. Escudier B, Porta C, Schmidinger M, Rioux-Leclercq N, Bex A, Khoo V, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.*2019;30(5):706-720.

27. Motzer RJ, Jonasch E, Agarwal N, Alva A, Baine M, Beckermann K, et al. Kidney Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.*2022;20(1):71-90. doi: 10.6004/jnccn.2022.0001

28. Jones J, Bhatt J, Avery J, Laupacis A, Coan K, Basappa N, et al. The kidney cancer research priority-setting partnership: Identifying the top 10 research priorities as defined by patients, caregivers, and expert clinicians. *Can Urol Assoc J.*2017;11(12):379-387. doi: 10.5489/cuaj.4590

29. Rossi SH, Blick C, Handforth C, Brown JE, Stewart GD; Renal Cancer Gap Analysis Collaborative. Essential research priorities in renal cancer: a modified Delphi Consensus Statement. *Eur Urol Focus.*2020 Sep 15;6(5):991-998. doi: 10.1016/j.euf.2019.01.014. Epub 2019 Feb 14.

30. Rossi SH, Fielding A, Blick C, Handforth C, et al. Setting research priorities in partnership with patients to provide patient-centred urological cancer care. *Eur Urol.*2019;75(6):891-893.

31. Rini B, Abel EJ, Albiges L, Bex A, Brugarolas J, Bukowski RM, et al. Summary from the Kidney Cancer Association's Inaugural Think Thank: Coalition for a Cure. *Clin Genitourin Cancer.*2021;19(2):167-175. doi: 10.1016/j.clgc.2020.10.005

32. The Kidney Cancer UK patient survey report 2018. Available at: https://www.kcuk.org.uk/2018/08/16/2018-kidney-cancer-patient-survey/. Accessed September 22, 2022.

33. Fenton JJ, Weiss NS. Screening computed tomography: will it result in overdiagnosis of renal carcinoma? *Cancer.*2004;100(5):986-990.

34. Cumberbatch MG, Rota M, Catto JW, La Vecchia C. The role of tobacco smoke in bladder and kidney carcinogenesis: a comparison of exposures and meta-analysis of incidence and mortality risks. *Eur Urol.*2016;70(3):458-466. doi: 10.1016/j.eururo.2015.06.042. Epub 2015 Jul 3.

35. Lotan Y, Karam JA, Shariat SF, Gupta A, Roupret M, Bensalah K, et al. Renal-cell carcinoma risk estimates based on participants in the prostate, lung, colorectal, and ovarian cancer screening trial and national lung screening trial. *Urol Oncol.*2016;34(4):167; e9- e16. doi: 10.1016/j.urolonc.2015.10.011. Epub 2015 Nov 18.

36. Hunt JD, van der Hel OL, McMillan GP, Boffetta P, Brennan P. Renal cell carcinoma in relation to cigarette smoking: meta-analysis of 24 studies. *Int J Cancer.*2005;114(1):101-108. doi: 10.1002/ijc.20618

37. Macleod LC, Hotaling JM, Wright JL, Davenport MT, Gore JL, Harper J, et al. Risk factors for renal cell carcinoma in the VITAL study. *J Urol.*2013;190(5):1657-1661. doi: 10.1016/j.juro.2013.04.130. Epub 2013 May 9.

38. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, et al. Body fatness and cancer--viewpoint of the IARC Working Group. *N Engl J Med.*2016;375(8):794-798. doi: 10.1056/NEJMsr1606602

39. Wang F, Xu Y. Body mass index and risk of renal cell cancer: a dose-response meta-analysis of published cohort studies. *Int J Cancer.*2014;135(7):1673-1686.

40. Hidayat K, Du X, Zou SY, Shi BM. Blood pressure and kidney cancer risk: meta-analysis of prospective studies. *J Hypertens.*2017;35(7):1333-1344.

41. Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. *Arch Intern Med.*2006;166(17):1871-1877. doi: 10.1001/archinte.166.17.1871.

42. Daniel CR, Schwartz KL, Colt JS, Dong LM, Ruterbusch JJ Purdue MP, et al. Meat-cooking mutagens and risk of renal cell carcinoma. *Br J Cancer.*2011 Sep 27;105(7):1096-104. doi: 10.1038/bjc.2011.343. Epub 2011 Sep 6.

43. Daniel CR, Cross AJ, Graubard BI, Park Y, Ward MH, Rothman N, et al. Large prospective investigation of meat intake, related mutagens, and risk of renal cell carcinoma. *Am J Clin Nutr.*2012;95(1):155-162. doi: 10.3945/ajcn.111.019364

44. Liu B, Mao Q, Wang X, Zhou F, Luo J, Wang C, et al. Cruciferous vegetables consumption and risk of renal cell carcinoma: a meta-analysis. *Nutr Cancer.*2013;65(5):668-676. doi: 10.1080/01635581.2013.795980.

45. Zhao J, Zhao L. Cruciferous vegetables intake is associated with lower risk of renal cell carcinoma: evidence from a meta-analysis of observational studies. *PLoS One.*2013;8(10):e75732.

46. Lew JQ, Chow WH, Hollenbeck AR, Schatzkin A, Park Y. Alcohol consumption and risk of renal cell cancer: the NIH-AARP diet and health study. *Br J Cancer.*2011;104(3):537-541. doi: 10.1038/sj.bjc.6606089. Epub 2011 Jan 18.

47. Jay R, Brennan P, Brenner, Overvad K, Olsen A, Tjønneland A, et al. Alcohol consumption and the risk of renal cancers in the European Prospective Investigation into Cancer and Nutrition (EPIC). Wozniak MB, Brennan P, Brenner DR, Overvad K, Olsen A, Tjonneland A, et al. *Int J Cancer.*2015 Oct 15;137(8):1953-1966. [Epub 2015 Apr 28]. doi: 10.1002/ijc.29559. *Urol Oncol.*2017 Mar;35(3):117. doi: 10.1016/j.urolonc.2016.12.022. Epub 2017 Feb 1.

48. Chiu WA, Caldwell JC, Keshava N, Scott CS. Key scientific issues in the health risk assessment of trichloroethylene. *Environ Health Perspect.*2006;114(9):1445-1449.

49. Scott CS, Chiu WA. Trichloroethylene cancer epidemiology: a consideration of select issues. *Environ Health Perspect.*2006;114(9):1471-1478.

50. Harth V, Bruning T, Bolt HM. Renal carcinogenicity of trichloroethylene: update, mode of action, and fundamentals for occupational standard setting. *Rev Environ Health.*2005;20(2):103-118.

51. Choueiri TK, Je Y, Cho E. Analgesic use and the risk of kidney cancer: a meta-analysis of epidemiologic studies. *Int J Cancer.*2014;134(2):384-396.

52. Clague J, Lin J, Cassidy A, Matin S, Tannir NM, Tamboli P, et al. Family history and risk of renal cell carcinoma: results from a case-control study and systematic meta-analysis. *Cancer Epidemiol Biomarkers Prev.*2009;18(3):801-807. doi: 10.1158/1055-9965.EPI-08-0601. Epub 2009 Feb 24.

53. Scelo G, Muller DC, Riboli E, Johannson M, Cross AJ, Vineis P, et al. KIM-1 as a blood-based marker for early detection of kidney cancer: a prospective nested case-control study. *Clin Cancer Res.*2018 Nov 15;24(22):5594-5601. doi: 10.1158/1078-0432.CCR-18-1496

54. Wilson JM, Jungner YG. Principles and practice of mass screening for disease [article in Spanish]. *Bol Oficina Sanit Panam.*1968;65(4):281-393.

55. Harvey-Kelly LLW, Harrison H, Rossi SH, Griffin SJ, Stewart GD, Usher-Smith JA. Public attitudes towards screening for kidney cancer: an online survey. *BMC Urol.*2020;20(1):170. doi: 10.1186/s12894-020-00724-0

56. Rossi SH, Prezzi D, Kelly-Morland C, Goh V. Imaging for the diagnosis and response assessment of renal tumours. *World J Urol.*2018;36(12):1927-1942.

57. Millet I, Doyon FC, Hoa D, Thuret R, Merigeaud S, Serre I, et al. Characterization of small solid renal lesions: can benign and malignant tumors be differentiated with CT? *AJR Am J Roentgenol.*2011;197(4):887-896. doi: 10.2214/AJR.10.6276

58. Marconi L, Dabestani S, Lam TB, Hofmann F, Stewart F, Norrie J, et al. Systematic review and meta-analysis of diagnostic accuracy of percutaneous renal tumour biopsy. *Eur Urol.*2016;69(4):660-673. doi: 10.1016/j.eururo.2015.07.072. Epub 2015 Aug 29.

59. Patel HD, Druskin SC, Rowe SP, Pierorazio PM, Gorin MA, Allaf ME. Surgical histopathology for suspected oncocytoma on renal mass biopsy: a systematic review and meta-analysis. *BJU Int.*2017;119(5):661-666. doi: 10.1111/bju.13763. Epub 2017 Feb 27.

60. Kim JH, Li S, Khandwala Y, Chung KJ, Park HK, Chung BI. Association of prevalence of benign pathologic findings after partial nephrectomy with preoperative imaging patterns in the United States From 2007 to 2014. *JAMA Surg.*2019;154(3):225-231.doi: 10.1001/jamasurg.2018.4602.

61. Johnson DC, Vukina J, Smith AB, Meyer AM, Wheeler SB, Kuo t-M, et al. Preoperatively misclassified, surgically removed benign renal masses: a systematic review of surgical series and United States population level burden estimate. *J Urol.*2015;193(1):30-35. doi: 10.1016/j.juro.2014.07.102. Epub 2014 Jul 27.

62. Pierorazio PM, Johnson MH, Ball MW, Gorin MA, Trock BJ, Chang P, et al. Five-year analysis of a multi-institutional prospective clinical trial of delayed intervention and surveillance for small renal masses: the DISSRM registry. *Eur Urol.*2015;68(3):408-415. doi: 10.1016/j.eururo.2015.02.001. Epub 2015 Feb 16.

63. Khadhouri S, Gallagher KM, MacKenzie KR, Shah TT,Gao C, Moore S, et al. The IDENTIFY study: the investigation and detection of urological neoplasia in patients referred with suspected urinary tract cancer - a multicentre observational study. *BJU Int.*2021;128(4):440-450. doi: 10.1111/bju.15483

64. Bangma CH, Loeb S, Busstra M, Zhu X, El Bouazzaoui S, Refos J, et al. Outcomes of a bladder cancer screening program using home hematuria testing and molecular markers. *Eur Urol.*2013;64(1):41-47. doi: 10.1016/j.eururo.2013.02.036

65. Messing EM, Madeb R, Young T, Gilchrist KW, Bram L, Greenberg EB, et al. Long-term outcome of hematuria home screening for bladder cancer in men. *Cancer.*2006;107(9):2173-2179. doi: 10.1002/cncr.22224

66. Sugimura K, Ikemoto SI, Kawashima H, Nishisaka N, Kishimoto T. Microscopic hematuria as a screening marker for urinary tract malignancies. *Int J Urol.*2001;8(1):1-5. doi: 10.1046/j.1442-2042.2001.00235.x

67. Sharp VJ, Barnes KT, Erickson BA. Assessment of asymptomatic microscopic hematuria in adults. *Am Fam Physician.*2013;88(11):747-754.

68. Flitcroft JG, Verheyen J, Vemulkar T, Welbourne EN, Rossi SH, Wlesh SJ, et al. Early detection of kidney cancer using urinary proteins: a truly non-invasive strategy. *BJU Int.* 2022 Mar;129(3):290-303. doi: 10.1111/bju.15601. Epub 2021 Nov 3.

69. Morrissey JJ, Mellnick VM, Luo J, Siegel MJ, Figenshau RS, Bhayani S, et al. Evaluation of urine aquaporin-1 and perilipin-2 concentrations as biomarkers to screen for renal cell carcinoma: a prospective cohort study. *JAMA Oncol.*2015;1(2):204-212. 10.1001/jamaoncol.2015.0213

70. Klein EA, Richards D, Cohn A, Tummala M, Lapham R, Cosgrove D, et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. *Ann Oncol.*2021;32(9):1167-1177. doi: 10.1016/j.annonc.2021.05.806.

71. Nadauld LD, McDonnell CH 3rd, Beer TM, Liu MC, Klein EA, Hudnut A, et al. The PATHFINDER Study: assessment of the implementation of an investigational multi-cancer early detection test into clinical practice. *Cancers (Basel).*2021 Jul 13;13(14):3501. doi: 10.3390/cancers13143501.

72. The NHS Galleri Test. Available at: https://www.nhs-galleri.org/. Accessed September 22, 2022.

73. Chen X, Gole J, Gore A, He Q, Lu M, Min J, et al. Non-invasive early detection of cancer four years before conventional diagnosis using a blood test. *Nat Commun.*2020 Jul 21;11(1):3475. doi: 10.1038/s41467-020-17316-z

74. Liu MC, Oxnard GR, Klein EA, Swanton C, Seiden MV; CCGA Consortium. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Ann Oncol.*2020;31(6):745-759. doi: 10.1016/j.annonc.2020.02.011. Epub 2020 Mar 30.

75. Rossi SH, Stewart GD. Re: clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. *Eur Urol.*2022;82(4):442-443.

76. Smith CG, Moser T, Mouliere F, Field-Rayner J, Eldridge M, Riediger AL, et al. Comprehensive characterization of cell-free tumor DNA in plasma and urine of patients with renal tumors. *Genome Med.*2020;12(1):23. doi: 10.1186/s13073-020-00723-8

77. Nuzzo PV, Berchuck JE, Korthauer K, Spisak S, Nassar AH, Abou Alaiwi S, et al. Detection of renal cell carcinoma using plasma and urine cell-free DNA methylomes. *Nat Med.*2020;26(7):1041-1043. doi: 10.1038/s41591-020-0933-1. Epub 2020 Jun 22.

78. Rossi SH, Hsu R, Blick C, Goh V, Nathan P, Nicol D, et al. Meta-analysis of the prevalence of renal cancer detected by abdominal ultrasonography. *Br J Surg.*2017;104(6):648-659. doi: 10.1002/bjs.10523

79. Spouge AR, Wilson SR, Wooley B. Abdominal sonography in asymptomatic executives: prevalence of pathologic findings, potential benefits, and problems. *J Ultrasound Med.*1996;15(11):763-767; quiz 9-70.

80. Fujii Y, Ajima J, Oka K, Tosaka A, Takehara Y. Benign renal tumors detected among healthy adults by abdominal ultrasonography. *Eur Urol.*1995;27(2):124-127. doi: 10.1159/000475142

81. Mihara S, Kuroda K, Yoshioka R, Koyama W. Early detection of renal cell carcinoma by ultrasonographic screening--based on the results of 13 years screening in Japan. *Ultrasound Med Biol.*1999;25(7):1033-1039.

82. Tsuboi N, Horiuchi K, Kimura G, Kondoh Y, Yoshida K, Nishimura T, et al. Renal masses detected by general health checkup. *Int J Urol.*2000;7(11):404-408. doi: 10.1046/j.1442-2042.2000.00220.x

83. Mizuma Y, Watanabe Y, Ozasa K, Hayashi K, Kawai K. Validity of sonographic screening for the detection of abdominal cancers. *J Clin Ultrasound.*2002;30(7):408-415. doi: 10.1002/jcu.10089

84. Filipas D, Spix C, Schulz-Lampel D, Michaelis J, Hohenfellner R, Roth S, et al. Screening for renal cell carcinoma using ultrasonography: a feasibility study. *BJU Int.*2003;91(7):595-599. doi: 10.1046/j.1464-410x.2003.04175.x

85. Malaeb BS, Martin DJ, Littooy FN, Lotan Y, Waters WB, Flanigan RC, et al. The utility of screening renal ultrasonography: identifying renal cell carcinoma in an elderly asymptomatic population. *BJU Int.*2005;95(7):977-981. doi: 10.1111/j.1464-410X.2005.05451.x

86. Warshauer DM, McCarthy SM, Street L, Bookbinder MJ, Glickman MG, Richter J, et al. Detection of renal masses: sensitivities and specificities of excretory urography/linear tomography, US, and CT. *Radiology.*1988;169(2):363-265. doi: 10.1148/radiology.169.2.3051112

87. Jamis-Dow CA, Choyke PL, Jennings SB, Linehan WM, Thakore KN, Walther MM. Small (< or = 3-cm) renal masses: detection with CT versus US and pathologic correlation. *Radiology.*1996;198(3):785-788. doi: 10.1148/radiology.198.3.8628872

88. The US preventive services task force Final Recommendation Statement on Abdominal Aortic Aneurysm Screening. updated 2019. Available at: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/abdominal-aortic-aneurysm-screening. Accessed September 22, 2022.

89. The National Health Service Abdominal Aortic Aneurysm Screening. Available at: https://www.nhs.uk/conditions/abdominal-aortic-aneurysm-screening/. Accessed September 22, 2022.

90. Wanhainen A, Bjorck M. The Swedish experience of screening for abdominal aortic aneurysm. *J Vasc Surg.*2011;53(4):1164-1165.

91. Pelc NJ. Recent and future directions in CT imaging. *Ann Biomed Eng.*2014;42(2):260-268.

92. Millor M, Bartolome P, Pons MJ, Bastarrika G, Beloqui O, Cano D, et al. Whole-body computed tomography: a new point of view in a hospital check-up unit? Our experience in 6516 patients. *Radiol Med.*2019;124(12):1199-1211. doi: 10.1007/s11547-019-01068-y. Epub 2019 Aug 12.

93. Beinfeld MT, Wittenberg E, Gazelle GS. Cost-effectiveness of whole-body CT screening. *Radiology.*2005;234(2):415-422.

94. Pickhardt PJ, Graffy PM, Perez AA, Lubner MG, Elton DC, Summers RM. Opportunistic screening at abdominal CT: use of automated body composition biomarkers for added cardiometabolic value. *Radiographics.*2021;41(2):524-542. doi: 10.1148/rg.2021200056

95. Crosbie PA, Gabe R, Simmonds I, Kennedy M, Rogerson S, Ahmed N, et al. Yorkshire Lung Screening Trial (YLST): protocol for a randomised controlled trial to evaluate invitation to community-based low-dose CT screening for lung cancer versus usual care in a targeted population at risk. *BMJ Open.*2020;10(9):e037075. doi: 10.1136/bmjopen-2020-037075

96. Rossi SH, Klatte T, Usher-Smith JA, Fife K, Welsh SJ, Dabestani S, et al. A decision analysis evaluating screening for kidney cancer using focused renal ultrasound. *Eur Urol Focus.*2021 Mar;7(2):407-419. doi: 10.1016/j.euf.2019.09.002. Epub 2019 Sep 14.

97. Harrison H, Thompson RE, Lin Z, Rossi SH, Stewart GD, Griffin SJ, et al. Risk prediction models for kidney cancer: a systematic review. *Eur Urol Focus.*2021 Nov;7(6):1380-1390. doi: 10.1016/j.euf.2020.06.024. Epub 2020 Jul 14

98. Harrison H, Pennells L, Wood A, Rossi SH, Stewart GD, Griffin SJ, et al. Validation and public health modelling of risk prediction models for kidney cancer using the UK Biobank. *BJU Int.*2022 Apr;129(4):498-511. doi: 10.1111/bju.15598. Epub 2021 Oct 7.

99. Harrison H, Li N, Saunders CL, Rossi SH, Dennis J, Griffin SJ, et al. The current state of genetic risk models for the development of kidney cancer: a review and validation. *BJU Int.*2022 Apr 22. doi: 10.1111/bju.15752. Online ahead of print.

100. Usher-Smith JA, Harvey-Kelly LLW, Rossi SH, Harrison H, Griffin SJ, Stewart GD. Acceptability and potential impact on uptake of using different risk stratification approaches to determine eligibility for screening: A population-based survey. *Health Expect.*2021 Apr;24(2):341-351. doi: 10.1111/hex.13175. Epub 2020 Dec 2.

101. Heleno B, Thomsen MF, Rodrigues DS, Jorgensen KJ, Brodersen J. Quantification of harms in cancer screening trials: literature review. *BMJ.*2013;347:f5334. doi: https://doi.org/10.1136/bmj.f5334

102. Harris RP, Sheridan SL, Lewis CL, Barclay C, Vu MB, Kistler CE, et al. The harms of screening: a proposed taxonomy and application to lung cancer screening. *JAMA Intern Med.*2014 Feb 1;174(2):281-5. doi: 10.1001/jamainternmed.2013.12745

103. Korenstein D, Chimonas S, Barrow B, Keyhani S, Troy A, Lipitz-Snyderman A. Development of a conceptual map of negative consequences for patients of overuse of medical tests and treatments. *JAMA Intern Med.* 2018;178(10):1401-1407. doi: 10.1001/jamainternmed.2018.3573jamainternmed.2018.3573