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Cancer Screening Recommendations for Solid Organ Transplant Recipients: A Systematic Review of Clinical Practice Guidelines

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Abbreviations

AASLD: American Association for the Study of Liver Disease

AGREE II: Appraisal of Guidelines Research and Evaluation II

AST: American Society of Transplantation

CPG: Clinical Practice Guideline

CSN: Canadian Society of Nephrology

CST: Canadian Society of Transplantation

EBPG: European Best Practice Guidelines

ISHLT: International Society of Heart and Lung Transplantation

KDIGO: Kidney Disease: Improving Global Outcomes

KHA-CARI: Kidney Health Australia-Caring for Australasians with Renal Impairment

LOE: Level of Evidence

NKF: National Kidney Foundation

RA: Renal Association Clinical Practice Guidelines

SOR: Strength of Recommendation

SOTR: Solid organ transplant recipient

SCPG: Swiss Clinical Practice Guidelines

Abstract

Solid organ transplant recipients (SOTRs) are at increased risk of developing and dying from cancer. However, controversies exist around cancer screening in this population due to reduced life expectancy and competing causes of death. This systematic review assesses the availability, quality, and consistency of cancer screening recommendations in clinical practice guidelines (CPGs). We systematically searched bibliographic databases and grey literature to identify CPGs and assessed their quality using AGREE-II. Recommendations were extracted along with their supporting evidence. Thirteen guidelines were included in the review. CPGs for kidney recipients were the most frequent source of screening recommendations, and recommendations for skin cancer screening were most frequently presented. Some screening recommendations differed from those of the general population, based on literature demonstrating higher cancer incidence among SOTRs vs. direct evidence of screening effectiveness. Relevant stakeholders such as oncology specialists, primary care providers, and public health experts were not involved in the formulation of the screening recommendations. In conclusion, although several guidelines make recommendations for cancer screening in SOTRs, the availability of cancer screening recommendations varied considerably by transplanted organ. More studies are required to inform cancer screening recommendations in SOTRs, and guideline development should involve transplant patients, oncologists, and cancer screening specialists.

Introduction

Malignancy is a leading cause of death among solid organ transplant recipients (SOTRs) (1-3). Transplant recipients are known to be at a higher risk of developing and dying of cancer compared to the general population, (4-7) and malignancies that develop in SOTRs are challenging to treat and have worse prognosis (8-11). Although early cancer diagnosis may improve cancer outcomes in this population, the reduced life expectancy and multiple comorbidities that exist in SOTRs make cancer screening controversial (12-18). No randomized controlled screening trials have been performed in SOTRs, and the performance of screening tests in this population is largely unknown (12).

Clinical practice guidelines (CPGs) provide valuable tools for evidence-based medicine by reviewing current research and creating recommendations based on available evidence (19). Given the limited available evidence for cancer screening in SOTRs, most recommendations generally parallel the guidelines available for the general population. A number of CPGs for long-term care of SOTRs issued by transplant organizations include various cancer screening recommendations; however, the quality of these guidelines, consistency of the recommendations, and supporting evidence is unknown. The purposes of this systematic review were to identify and assess the quality and consistency of cancer screening recommendations in CPGs for long-term care of SOTRs, and summarize evidence supporting these recommendations.

Methods

Search Strategy

A search strategy was designed in consultation with a senior information specialist for MEDLINE, EMBASE, CINAHL and PsycInfo databases from inception to January 2015 using variations on the search terms “cancer”, “screening”, and “transplantation” (**Appendix A**). Bibliographies of relevant literature were searched for additional resources. Grey literature (transplant organizations and Google Scholar) was also searched to retrieve additional records not found in the database search (organization websites searched in **Appendix B**).

Selection Criteria

Article titles, abstracts, and full-texts were independently screened by two researchers (AL, SM). To ensure consistency between reviewers, a random sample of 50 records was first independently assessed by each reviewer and the results were compared. Disagreement in greater than 10% of the sample initiated a review and edit of the criteria. Records were included if they were a CPG for SOTRs and included recommendations for malignancy screening. Records were

excluded if they focused on cancer screening in transplant candidates or organ donors, or focused on cancer surveillance of transplant recipients who underwent transplantation for a malignancy. Non-English resources were excluded due to restrictions on resources for translation.

Data Extraction

All data extraction was conducted independently by two reviewers. Data extracted included information on guideline author/organization, publication year, journal, region, transplant site, cancer screening site, target audience and population, as well as reference articles that were used as evidence to formulate cancer screening recommendation. Discrepancies between reviewers were resolved through discussion with a third reviewer (CD, SA) until consensus was achieved.

Quality Assessment

Three reviewers independently assessed the guidelines using the Appraisal of Guidelines Research and Evaluation II (AGREE-II) tool.(20) The AGREE-II tool assesses CPGs based on six domains using 24 questions on a 7 point scale. Disagreement among reviewers of > 2 points for each question were discussed and resolved by consensus.(21, 22) None required adjudication by an additional reviewer. The AGREE-II tool provides a mechanism for assigning each reviewed guideline with six quality scores; one for each domain. Under the Rigor of Development Domain, a link between recommendation and evidence would be considered present if the available evidence were based on studies that specifically examined cancer screening in SOTRs. The domain scores were calculated by summing up the individual reviewer scores in one domain and by scaling the sum as a percentage of the maximum possible score for that domain.(20)

Level of Evidence and Strength of Recommendation

Recommendations pertaining to post-transplant cancer screening were identified, and categorized by cancer screening and transplant organ sites. Information on the associated level of evidence (LOE) and strength of recommendations (SOR) was also extracted. There were variations in how individual guidelines provided grading scales on LOE and SOR. Hence a standardized grading scale was created and presented in **Appendix C**.

Results

The literature search identified 2,763 records collectively from MEDLINE, EMBASE, CINAHL, and PsycINFO. Removal of duplicates resulted in 2,117 unique records for review.

Following title and abstract screening, 149 articles remained in the review. An additional 57 were removed after full text review. Nine articles not found by the database search were identified from the reference lists of the eligible articles. Fifteen resources were identified from the grey literature search. Of the final 116 resources, 20 provided recommendations regarding malignancy screening as part of long-term, post-transplant health care. Of these, seven were excluded because they were commentaries and editorials where authors suggested cancer screening vs. CPGs. The remaining thirteen resources were considered CPGs and included in the review (**Figure 1**).

Characteristics of the CPGs

The characteristics of the reviewed CPGs are presented in **Table 1**. Five CPGs focused specifically on kidney transplant recipients including the Kidney Disease: Improving Global Outcomes (KDIGO);(23) Kidney Health Australia-Caring for Australasians with Renal Impairment (KHA-CARI); (24) American Society of Transplantation (AST) - Kidney;(25) European Best Practice Guidelines (EBPG) Guidelines;(26) and Renal Association Clinical Practice Guidelines (RA).(27) In addition, the updated European Renal Best Practice (ERBP) Advisory Board fully endorsed the KDIGO recommendations for cancer screening (28). The Canadian Society of Transplantation & Canadian Society of Nephrology (CST & CSN)(28), and National Kidney Foundation (NKF) (29) both adapted the recommendation for cancer screening from KDIGO. Three CPGs specifically focused on liver transplant patients including the American Association for the Study of Liver Disease (AASLD) – Adult (30); AASLD-Pediatric (31); and AST – Liver (32). One focused on heart-lung (International Society of Heart and Lung Transplantation, ISHLT) (31), and one was not limited to the type of organ transplant (Swiss Clinical Practice Guidelines, SCPG) (33). Five CPGs were developed in the United States, one was developed in the United Kingdom, two were developed in Europe, and two were from international organizations. Canada, Australia, and Switzerland were responsible for one CPG each.

Quality Assessment

The endorsement/adaptations of the KDIGO guidelines were not assessed as they did not constitute complete CPGs (28, 29). All CPGs scored well in domains 1 (scope and purpose) and 4 (clarity and presentation), and moderately in domain 2 (stakeholder involvement) (**Table 2**). The CPGs scored variably for domain 3 (rigor of development). Scores ranged from 10.1% (AST-Liver) to 78.3% (KDIGO). ISHLT, KDIGO, KHA-CARI, and AASLD-Pediatric explicitly presented both their systematic methods for evidence searches and their selection criteria. AASLD-Adult included partial

information on their evidence searches, while the original EBPg partially described their selection criteria. AST and AASLD were the only CPG to not explicitly discuss considerations of health benefits, side effects, and risks when creating CPG recommendations. Notably most CPGs did not present an explicit link between recommendation and evidence (EBPg, AST-Kidney, SCPG, AST-Liver, ISHLT, and AASLD-Pediatric). Only two CPGs were sent out to relevant professionals for external review prior to publication (CPGC, KDIGO). In general, the CPGs performed poorly on Domain 5 (applicability), with scores ranging from 0% (AASLD-Adult and RA) to 50% (KHA-CARI). KDIGO was the only CPGs to specifically address facilitators and barriers to screening. Resource implications, mostly in the form of cost-effectiveness considerations, were explicitly discussed by KHA-CARI and KDIGO, and partially covered by AASLD-Pediatric. KHA-CARI and the RA were the only two CPGs to offer specific criteria for monitoring or auditing. Lastly, although development groups for CPGs included professionals from both organ-specific and transplant specialties, they failed to include oncology specialists, primary care providers, or experts in public health/screening. All CPGs clearly defined the target users for their CPG, but none sought out or incorporated the views or preferences of the target patient population.

Guideline Recommendations for Cancer Screening

Recommendations for cancer screening among SOTRs are shown in **Table 3**. No CPG had specific recommendations for surveillance of pre-transplant malignancies.

Skin Malignancies: A total of ten CPGs provided specific recommendations on skin and lip cancer screening. Nine CPGs advise SOTRs undergo clinical exam on an annual basis. Among the nine CPGs, four recommend skin screening by a primary care physician (25, 29, 31, 32), while the remaining five CPGs specify that a dermatologist or specialist should perform the screening (23, 24, 30, 33). Additionally, the AST recommends additional risk stratification - patients at high risk due to susceptible skin type, history of high sun exposure, or history of skin health concerns undergo physician screening more frequently than yearly (25, 32). Regular self-exams in conjunction with physician or specialist exams are also recommended by several CPGs (23-25, 30).

Cervical Cancer: A total of eight CPGs provided specific recommendations on cervical cancer screening. KDIGO and RA recommend kidney recipients undergo Papanicolaou (PAP) cytology with pelvic exam every 3 years (23, 27), consistent with general population recommendations. CST & CSN, KHA-CARI, EBPg, AST-Kidney, and AST-Liver recommend more frequent screening than the general population (i.e., annual PAP cytology and pelvic exam) (24-26, 32). In contrast, AASLD-Adult recommends cervical cancer screening performed every 3 to 5 years (30).

Breast Cancer: A total of six CPGs provided specific recommendations on breast cancer screening. KDIGO, CST & CSN, and RA recommend SOTRs follow the general population guidelines. AST-Kidney recommends mammography every 1 to 2 years (25), while EBPg recommends mammography with no specific frequency.(26)

Prostate Cancer: A total of seven CPGs provided specific recommendations on prostate cancer screening. Four CPGs follow the general population guidelines and advise SOTRs not undergo prostate cancer screening. In contrast, AST-Kidney, EBPg, and AST-Liver recommend annual prostate-specific antigen (PSA) testing and digital rectal exam (DRE) for male patients 50 or older with at least a 10 year expected lifespan (25, 26, 32).

Renal and Urothelial Malignancies: Screenings for kidney (27) and bladder/urothelial (25) cancer among kidney recipients are not recommended by the AST-Kidney (25) and RA (27) respectively. Only EBPg recommends ultrasound screening for native kidney cancer among kidney recipients (26).

Liver Malignancies: A total of six CPGs provided specific recommendations on liver cancer screening in kidney recipients. Patients with cirrhosis, liver disease, or those who are at high risk (HBV- or HCV-infected recipients) are recommended to undergo serum alpha-fetoprotein (AFP) and ultrasound screening every 6 to 12 months (23, 25, 27).

Colorectal Cancer: Among seven CPGs that provided specific recommendations on colorectal cancer screening, five follow general population recommendations (23, 25, 27, 31), one recommends only fecal occult blood tests (FOBT) with no specific screening frequency (26), and one recommends only annual colonoscopy for liver recipients with primary sclerosing cholangitis and inflammatory bowel disease or other established risk factors for colorectal cancer (30).

Other Malignancies: Screening for lung cancer among kidney recipients is recommended against by AST-Kidney (25). Kidney SOTRs are recommended to have a complete history and physical exam for indications of lymphomas every three months during the first post-transplant year, and then annually thereafter (25). Self-exam is recommended by RA for screening of testicular cancer (27).

Level of Evidence and Strength of Recommendation

LOE and SOR extracted from eligible CPGs are presented in **Table 4**. In general, CPGs recommendations were based on the authors' interpretation of the available literature, particularly findings that reported higher cancer incidence among SOTRs. Performance of screening tests and cancer treatment efficacy were often not explicitly mentioned when formulating the

recommendations. Older CPGs included more recommendations based solely on expert opinion and rated the level of evidence and strength of the recommendations higher. However, in recognition of the lack of evidence on screening trials in the transplant population, more recent CPGs such as KDIGO, CST & CSN, and KHA-CARI are more conservative with regards to making recommendations and grading evidence. For skin cancer, LOE, and SOR were given by most CPGs; recommendations were mostly rated as based on low and very low quality of evidence. Notably AST and AASLD considered the quality of evidence as “high” although only indirect evidence (e.g., RCTs in the general population, population-based studies on cancer incidence in SOTRs) was cited. Six CPGs did not evaluate LOE and SOR for other types of cancer screening. In the remaining CPGs, recommendations were based on variable quality of evidence. Evidence cited by the CPGs includes studies that examined cancer incidence, pathophysiology, risk factors, outcomes and treatment in the transplant population, and cancer screening trials or screening recommendations for the general population. Very few studies cited by the CPGs evaluated the performance of specific cancer screening tests in the transplant population. Moreover, a small number of CPGs recommended an individualized approach to cancer screening in SOTR, considering life expectancy and competing causes of death.

Discussion

This systematic review identified thirteen CPGs for post-transplant care that include recommendations for cancer screening. However, several weaknesses are present in the available recommendations. First, there is a lack of direct evidence to support cancer screening recommendations. Although screening for skin cancer is addressed in almost all CPGs reviewed, the inclusion of screening recommendations for other malignancies was variable. Most of the recommendations for cancer screening are targeted towards kidney recipients and fewer recommendations exist for other solid organ transplant recipients. Lastly, relevant stakeholders such as oncology specialists, primary care providers, and public health experts were not involved in the formulation of the screening recommendations.

Clinical skin examination (CSE) is not recommended for the general population and the evidence of a survival benefit of population-based screening is limited and restricted to the detection of early-stage melanoma in certain populations (34, 35). The benefit of screening for non-melanoma and melanoma skin malignancies with CSE is based on the presumption that early detection and treatment will reduce the morbidity and mortality of skin cancer, and that examination by a qualified health professional can detect skin cancer early. As SOTRs are at

increased risk of developing and dying from non-melanoma and melanoma skin malignancies (36, 37), annual screening for skin cancer with clinical skin examination (CSE) is uniformly recommended for all SOTRs, and some CPGs specify the CSE should be performed by a dermatologist or trained physician.

Although recommendations for breast, colorectal, cervical, and prostate cancer screening were often the same as those for the general population, some CPGs recommend earlier and more frequent screening because of a perceived increased incidence in SOTRs. However, consistent evidence of increased incidence in SOTRs only exists for colorectal cancer (36, 37). Differences between CPGs in the screening recommendations for prostate cancer likely reflect changes over time in the recommendations for screening in the general population. Screening for lung and renal malignancies is not recommended among kidney recipients. The only CPG that evaluated lung cancer screening recommended against it in 2000 (25). However, given recent evidence that supports the use of low-dose CT scan for lung cancer screening (38-40), a re-evaluation of the role for this modality of lung cancer screening would be timely. In the case of renal cancer, there is no evidence of benefit for screening in the general population. Despite the higher risk of renal cancer among kidney recipients, most guidelines recommend against or do not include a recommendation for renal cancer screening due to the very limited evidence available. A recent decision analysis explored the benefits and harms of biennial ultrasonography for screening of renal cancer in the kidney transplant population and showed screening did not provide benefits to patients (41).

Very few CPGs addressed reduced life expectancy and competing causes of death when formulating cancer screening recommendations. For the general population, cancer screening is less likely to benefit patients with life-threatening comorbidities or those with less than 5 or 10 years of a life expectancy, as the screening procedure may result in more harm than benefit (38, 42). Given that screening involves testing patients who are asymptomatic to find disease, strong evidence (e.g., based on randomized controlled trials) is needed to support screening interventions (23). However, randomized controlled trials of screening have not been performed in SOTRs and are unlikely to be undertaken because of major feasibility issues. Current cancer screening recommendations for SOTRs are based on extrapolation of findings from screening trials in the general population, as well as evidence of increased incidence of cancer and cancer-related mortality among SOTRs. Although some decision analysis models have been used to explore cancer screening in transplant recipients (15, 43), these models are limited by the scarce evidence on the performance of screening tests in transplant recipients and the outcomes (by stage at diagnosis) of transplant recipients who develop malignancy.

Although no CPG included tailored cancer screening recommendations, it is likely that certain subgroups of transplant recipients that are at increased risk of malignancy such as recipients with pre-transplant malignancies, history of hepatitis B or C infection might require specific screening approaches (44, 45). Moreover, in line with the cancer screening recommendations for the general population, individual risk factors (family history, smoking history, etc.) should be factored into the screening recommendations. Similarly, specific recommendations for surveillance of pre-transplant malignancies are needed as these patients are at increased risk of cancer death (44).

Another notable gap is that CPGs did not involve relevant stakeholders such as oncology specialists, primary care providers, and public health experts in the formulation of the screening recommendations. Participation of relevant stakeholders is essential to appropriately assess the evidence and formulate workable recommendations (46). In addition, none CPGs included sought or incorporated the perspectives of the SOTRs target population. Consideration of patients' preferences and values has been advocated in the development of CPG and has been associated with enhanced uptake of recommendations.(47, 48)

Strengths of this systematic review include the appraisal of the guidelines using AGREE II, a validated and reliable instrument, and categorization of literature to formulate the recommendations, which provided additional context to the level of evidence and strength of recommendation assessment. However, our systematic review also has some limitations. We included only those guidelines published in English. Previous research suggests exclusion of resources in languages other than English does not significantly influence the results of systematic reviews and meta-analyses.(49, 50) For this systematic review, we assessed guidelines based on all available information and/or literature from a recommending body. This included supplemental patient education resources such as pamphlets or websites, clinical guidelines for health care professionals, and formal publications. If the CPGs and their accompanying resources lacked information regarding specific AGREE II domain questions (e.g. literature search criteria or makeup of guideline development groups), we did not contact recommending bodies to verify these questions. It is possible that guideline development was undertaken in some of these cases with more rigor than the resources described. However, our purpose was to assess the guidelines generally available to the transplant health care community, and the design of the AGREE II tool is to assess the quality of reporting and dissemination of data. It is not standard practice when using AGREE-II to contact authors of CPGs to verify what was not included in their manuscript, and we followed that precedent (51, 52).

In conclusion, while there are some established recommendations for cancer screening in SOTRs, recommendations vary between organizations and are generally limited to kidney recipients. Although there was consensus on the recommendations for skin cancer screening and the extension of all existing cancer screening recommendations in general population to SOTRs, recommendations for screening in other malignancies were highly variable. Future CPG should incorporate consensus of experts (including oncologists, public health specialists, and patients) and integrate the results of decision-analysis models, that take into account the performance of the screening test in SOTRs based on their expected life expectancy and competing risk of death. Considering the increased burden of cancer mortality in SOTRs, additional effort needs to be directed towards formulating evidence-based cancer screening recommendations for this high-risk population.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Figure Legends

Figure 1. PRISMA Flow chart of article selection

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Appendix A: Search Strategies

Appendix B: List of sources included in the grey literature search.

Appendix C: Standardized scale on level of evidence and strength of recommendations.

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Table 1. Characteristics of the included clinical practice guidelines.

Guidelines	Region	Recommending Body Type	Funding Body	Transplanted Organ	Cancer Screening	Target Users
KDIGO (2009)(23)	International	Non-profit health organization	External funding for guideline development not allowed	Kidney	Skin/Lip, Cervical, Breast, Prostate, CRC, Liver, RCC	Transplant care medical professionals
ERBP* (2011)(28)	Europe	Professional society	Astellas, Hoffman-Laroche, Novartis, Amgen, Leo Pharmaceuticals, Fresenius Medical Care, SHIRE	Kidney	NS	Transplant care medical professionals
CST & CSN** (2010)(28)	Canada	Professional society	Self-funded	Kidney	Skin/Lip, Cervical, Breast, Prostate, CRC, Liver	Healthcare professionals
NKF** (2009)(29)	USA	Non-profit health organization	Not reported	Kidney	Skin/Lip	Healthcare professionals
KHA-CARI (2012)(24)	Australia	Professional society	Self-funded	Kidney	Skin/Lip, Cervical, Breast, Prostate, CRC,	Transplant care medical professionals

Liver, RCC						
AASLD-Adult (2013)(30)	USA	Professional society	Self-funded	Liver	Cervical, Skin, CRC	Physicians and health care providers
AASLD-Pediatric (2013)(31)	USA	Professional society	Self-funded	Liver	Skin, CRC	Physicians and health care providers
AST-Kidney (2000)(25)	USA	Professional society	External funding for guideline development not allowed	Kidney	Skin, Cervical, Breast, CRC, Prostate, Lung, PTLN, Urothelial, HCC	Physicians and other health care workers
AST-Liver (2009)(32)	USA	Professional society	External funding for guideline development not allowed	Liver	Cervical, Liver, PTLN, Urothelial	Primary care physicians
EBPG (2002)(26)	Europe	Professional society	Hoffman-La Roche AG	Kidney	Kidney, Prostate, Cervical, Breast, CRC	"All those active in the field of transplantation"
ISHLT (2010)(31)	International	Professional society	Self-funded	Heart/Lung	Breast, Prostate, Skin, CRC	Healthcare providers
RA (2011)(27)	UK	Professional	External funding	Kidney	Cervical, Breast,	Non-transplant-

		society	for guideline development not allowed		CRC, Prostate, RCC, Testicular, Skin/Lip	expert health care professionals
SCPG (2009)(33)	Switzerland	Professional societies	Not reported	All	Skin	Swiss Physicians

*Endorsement of the Kidney Disease: Improving Global Outcomes Guidelines

**Adaptation of the Kidney Disease: Improving Global Outcomes Guidelines

Abbreviations: KDIGO, Kidney Disease Improving Global Outcomes; ERBP, European Renal Best Practice; CST & CSN, Canadian Society of Transplantation and Canadian Society of Nephrology; KHA-CARI, Kidney Health Australia-Caring for Australasians with Renal Impairment; NKF, National Kidney Foundation; AASLD, American Association for the Study of Liver Disease; AST, American Society of Transplantation; EBPG, European Best Practice Guidelines; ISHLT, International Society of Heart & Lung Transplantation; RA, Renal Association Clinical Practice Guidelines; SCPG, Swiss Clinical Practice Guidelines; USA, United States of America; UK, United Kingdom; CRC, Colorectal Cancer; RCC, Renal Cell Carcinoma; PTLD, Post-Transplant Lymphoproliferative Disorder; HCC, Hepatocellular Carcinoma; TR, Transplant Recipients; NS, not specified.

Table 2. Domain scores of the included clinical practice guidelines according to the AGREE-II instrument.

Guideline	Domain (%)					
	Scope and Purpose	Stakeholder Involvement	Rigor of Development	Clarity of Presentation	Applicability	Editorial Independence
KDIGO(23)	80	63	78	80	37	97
KHA-CARI(24)	91	42	66	94	50	100
AASLD-Adult(30)	91	56	38	69	0	50
AASLD-Pediatric(31)	89	61	71	56	21	42

AST-Kidney(25)	100	54	64	63	14	0
AST-Liver(32)	94	63	10	98	18	72
EBPG(26)	89	39	46	91	1	6
ISHLT(31)	100	63	62	74	1	100
RA(27)	93	48	33	61	0	28
SCPG(33)	96	57	20	72	28	25

Abbreviations: KDIGO, Kidney Disease Improving Global Outcomes; CST & CSN, Canadian Society of Transplantation and Canadian Society of Nephrology; KHA-CARI, Kidney Health Australia-Caring for Australasians with Renal Impairment; NKF, National Kidney Foundation; AASLD, American Association for the Study of Liver Disease; AST, American Society of Transplantation; EBPG, European Best Practice Guidelines; ISHLT, International Society of Heart & Lung Transplantation; RA, Renal Association Clinical Practice Guidelines; SCPG, Swiss Clinical Practice Guidelines.

Content of AGREE-II [extracted from Brouwers *et al.*(30)]:

The AGREE II consists of 23 key items organized within 6 domains. Each domain captures a unique dimension of guideline quality.

Domain 1. Scope and Purpose is concerned with the overall aim of the guideline, the specific health questions, and the target population.

Domain 2. Stakeholder Involvement focuses on the extent to which the guideline was developed by the appropriate stakeholders and represents the views of its intended users.

Domain 3. Rigour of Development relates to the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them.

Domain 4. Clarity of Presentation deals with the language, structure, and format of the guideline.

Domain 5. Applicability pertains to the likely barriers and facilitators to implementation, strategies to improve uptake, and resource implications of applying the guideline.

Domain 6. Editorial Independence is concerned with the formulation of recommendations not being unduly biased with competing interests.

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Table 3. Recommendations identified in clinical practice guidelines by cancer site and transplant organ.

Screening	Kidney							Liver			Heart/ Lung	All Solid Organ
	KDIGO (2009)	CST & CSN (2010)	NKF (2009)	KHA-CARI (2012)	AST- Kidney (2000)	EBPG (2002)	RA (2011)	AST-Liver (2009)	AASLD- Adult (2013)	AASLD- Pediatric (2013)	ISHLT (2010)	SCPG (2009)
Skin/Lip Cancer												
Self-exam	R	R	-	R	Monthly	-	-	-	R	-	-	-
Physician exam	-	-	Annually	-	Annually	-	R	Annually	-	NS	Annually	-
Specialist exam	Annually	Annually	-	Annually	-	-	-	-	Annually		-	Annually
Anal/Anogenital Cancer												
Physician exam	-	-	-	-	Annually	-	-	-	-	-	-	-
Testicular Cancer												
Self-exam	-	-	-	-	-	-	R	-	-	-	-	-
Cervical Cancer												
Pelvic exam	G (Every 3 years) ¹	-	-	Annually	Annually	Annually	G (Every 3 years) ¹	Annually	Every 3-5 years	-	-	-
PAP cytology	G (Every 3 years)	Annually	-	-	Annually	Annually	G (Every 3 years) ¹	Annually	Every 3-5 years	-	-	-
Breast Cancer												
Mammography	G (Annually)**	G (Every 2 years)*	-	-	Every 1-2 years	R	G (Every 3 years) ¹	-	-	-	G	-
Self-exam	-	-	-	-	-	-	R	-	-	-	-	-
Prostate Cancer												
PSA	-	-	-	-	Annually*	Annually*	-	Annually*	-	-	-	-

DRE	-	-	-	-	Annually*	Annually*	-	Annually*	-	-	-	-
Not recommended	G	G	-	-	-	-	G	-	-	-	G	-
Lung Cancer												
Not recommended	-	-	-	-	R	-	-	-	-	-	-	-
Kidney Cancer												
Ultrasound	-	-	-	-	-	R	-	-	-	-	-	-
Not recommended	-	-	-	-	-	-	R	-	-	-	-	-
Bladder/ Urothelial Cancer												
Not recommended	-	-	-	-	R	-	-	-	-	-	-	-
Liver/HCC												
AFP level	Annually‡	Annually‡	-	-	Every 6-12 months§	-	Annually‡	-	-	-	-	-
Ultrasound	Annually‡	Annually‡	-	-	Every 6-12 months‡‡	-	Annually‡	-	-	-	-	-
Abdominal imaging	-	-	-	-	-	-	-	-	-	-	-	-
Colorectal Cancer												
FOBT	G (Annually) or	G (Annually) or	-	-	G (Annually)*	R	G	-	-	-	G	-
Sigmoidoscopy	G (Every 5 years) or	G (Every 5 years) or	-	-	G (Every 5 years)*	-	G	-	-	-	G	-
Colonoscopy	G (Every 10 years)	G (Every 10 years)	-	-	-	-	G	-	Annually‡‡	NS	G	-
Lymphomas												
Physician exam	-	-	-	-	Every 3	-	-	-	-	-	-	-

	months in 1 st year, then annually			
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Abbreviations: KDIGO, Kidney Disease Improving Global Outcomes; CST & CSN, Canadian Society of Transplantation and Canadian Society of Nephrology; KHA-CARI, Kidney Health Australia-Caring for Australasians with Renal Impairment; NKF, National Kidney Foundation; AASLD, American Association for the Study of Liver Disease; AST, American Society of Transplantation; EBPG, European Best Practice Guidelines; ISHLT, International Society of Heart & Lung Transplantation; RA, Renal Association Clinical Practice Guidelines; SCPG, Swiss Clinical Practice Guidelines; PSA, Prostate- Specific Antigen; DRE, Digital Rectal Exam; PAP, Papanicolaou; HCC, Hepatocellular Carcinoma; AFP, Alpha-Fetoprotein; CRC, Colorectal Cancer; FOBT, Fecal Occult Blood Test; NS, non-specific modality.

Notations:

R Screening recommended but no frequency.

* Only for patients over 50 year-old

** Only for patients over 40 year-old

‡ Only for patients with cirrhosis

‡‡ Only for patients at high risk

§ Only for patients with liver disease

G Same as the guidelines from the general population

Table 4. Level of evidence and strength of recommendations reported in clinical practice guideline recommendations.

Screening	Kidney							Liver			Heart/Lung	All SOTR
	KDIGO	CST&CSN	NKF	KHA-CARI	AST-Kidney	EBPG	RA	AST-Liver	AASLD-Adult	AASLD-Pediatric	ISHLT	SCPG
Skin/Lip Cancer												
Self-exam	WR/D	WR/D	-	WR/D	NG/B	-	-	-	NG/NG	-	-	-
Physician exam	-	-	WR/D	-	NG/B	-	WR/C	NG/NG	-		SR/C	-
Specialist exam	WR/D	WR/D	-	WR/D	-	-	-	-	SR/A	SR/B	-	NG/D
Anal/Anogenital Cancer												
Physician exam	-	-	-	-	NG/A	-	-	-	-	-	-	-
Testicular Cancer												
Self-exam	-	-	-	-	-	-	WR/D	-	-	-	-	-
Cervical Cancer												
Pelvic exam	NG/NG	-	-	-	NG/A	NG/B	WR/C	NG/NG	NG/NG	-	-	-
PAP cytology	NG/NG	NG/NG	-	-	NG/A	NG/B	WR/C	NG/NG	NG/NG	-	-	-
Breast Cancer												
Mammography	NG/NG	NG/NG	-	-	NG/A-C	NG/B	WR/C	-	-	-	SR/C	-
Self-exam	-	-	-	-	-	-	WR/D	-	-	-	-	-
Prostate Cancer												
PSA	-	-	-	-	NG/C	NG/B	-	NG/NG	-	-	-	-
DRE	-	-	-	-	NG/C	NG/B	-	NG/NG	-	-	-	-
Not recommended	NG/NG	NG/NG	-	-	-	-	WR/C	-	-	-	SR/C	-

Lung Cancer												
Not recommended	-	-	-	-	NG/C	-	-	-	-	-	-	-
Kidney Cancer												
Ultrasound	-	-	-	-	-	NG/B	-	-	-	-	-	-
Not recommended	-	-	-	-	-	-	WR/C	-	-	-	-	-
Bladder/Urothelial Cancer												
Not recommended	-	-	-	-	NG/C-D	-	-	-	-	-	-	-
Liver/HCC												
AFP level	NG/NG	NG/NG	-	-	NG/C	-	2C	NG	-	-	-	-
Ultrasound	NG/NG	NG/NG	-	-	NG/C	-	2C	NG	-	-	-	-
Abdominal imaging	-	-	-	-	-	-	-	-	SR/A	-	-	-
CRC												
FOBT	NG/NG	NG/NG	-	-	NG/A	NG/B	WR/C	-	-		SR/C	-
Sigmoidoscopy	NG/NG	NG/NG	-	-	NG/A	-	WR/C	-	-	WR/B	SR/C	-
Colonoscopy	NG/NG	NG/NG	-	-	-	-	WR/C	-	SR/B		SR/C	-
Lymphomas												
Physician exam	-	-	-	-	NG/B	-	-	-	-	-	-	-

A standardized scale on level of evidence and strength of recommendations is presented in Appendix C.

Abbreviations: SR, Strong Recommendation | WR: Weak Recommendation | NG: Not Graded

KDIGO, Kidney Disease Improving Global Outcomes; CST & CSN, Canadian Society of Transplantation and Canadian Society of Nephrology; KHA-CARI, Kidney Health Australia-Caring for Australasians with Renal Impairment; NKF, National Kidney Foundation; AASLD, American Association for the Study of Liver Disease; AST, American Society of Transplantation; EBPg, European Best Practice Guidelines; ISHLT, International Society of Heart & Lung Transplantation; RA, Renal Association Clinical Practice Guidelines; SCPG, Swiss Clinical Practice Guidelines; DRE, Digital Rectal Exam; PAP, Papanicolaou; HCC, Hepatocellular Carcinoma; AFP, Alpha-Fetoprotein; CRC, Colorectal Cancer; FOBT, Fecal Occult Blood Test.

Identification

Screening

Eligibility

Included

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