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Release date: September 10, 2020; Expiration date: September 10, 2021

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Kidney Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Kidney Cancer

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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To view all of the conflicts of interest for the NCCN Guidelines panel, go to [NCCN.org/disclosures/guidelinepanellisting.aspx](https://www.nccn.org/disclosures/guidelinepanellisting.aspx).

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Kidney Cancer, Version 1.2021

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Kidney Cancer provide multidisciplinary recommendations for diagnostic workup, staging, and treatment of patients with renal cell carcinoma (RCC). These NCCN Guidelines Insights focus on recent updates to the guidelines, including changes to certain systemic therapy recommendations for patients with relapsed or stage IV RCC. They also discuss the addition of a new section to the guidelines that identifies and describes the most common hereditary RCC syndromes and provides recommendations for genetic testing, surveillance, and/or treatment options for patients who are suspected or confirmed to have one of these syndromes.

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	Preferred regimens	Other recommended regimens	Useful in certain circumstances
Favorable ^a	<ul style="list-style-type: none"> • Axitinib + pembrolizumab^b • Pazopanib • Sunitinib 	<ul style="list-style-type: none"> • Ipilimumab + nivolumab^b • Axitinib + avelumab^b • Cabozantinib (category 2B) 	<ul style="list-style-type: none"> • Active surveillance^c • Axitinib (category 2B) • High-dose IL-2^d
Poor/intermediate ^a	<ul style="list-style-type: none"> • Ipilimumab + nivolumab^b (category 1) • Axitinib + pembrolizumab^b (category 1) • Cabozantinib 	<ul style="list-style-type: none"> • Pazopanib • Sunitinib • Axitinib + avelumab^b 	<ul style="list-style-type: none"> • Axitinib (category 2B) • High-dose IL-2^d • Temsirolimus^e

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY		
Preferred regimens	Other recommended regimens	Useful in certain circumstances
<ul style="list-style-type: none"> • Cabozantinib (category 1) • Nivolumab^b (category 1) • Ipilimumab + nivolumab^b 	<ul style="list-style-type: none"> • Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Axitinib + pembrolizumab^b • Everolimus • Pazopanib • Sunitinib • Axitinib + avelumab^b (category 3) 	<ul style="list-style-type: none"> • Bevacizumab^f (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients^d (category 2B) • Temsirolimus^e (category 2B)

^a See Risk Models to Direct Treatment (IMDC criteria or MSKCC Prognostic Model) (KID-D).

^b See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

^c Rini BI, Dorr TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. *Lancet Oncol* 2016;17:1317-1324.

^d Patients with excellent performance status and normal organ function.

^e The poor risk model used in the global ARCC trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin <LLN, corrected calcium >10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007;356:2271-2281.

^f An FDA-approved biosimilar is an appropriate substitution for bevacizumab.

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KID-C
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Overview

An estimated 73,800 new cases of cancers of the kidney and renal pelvis will be diagnosed in the United States in 2020, and 14,800 people will die of the disease.¹ Approximately 85% of all kidney tumors are renal cell carcinoma (RCC), and approximately 70% of RCC cases are of clear cell histology (ccRCC).^{2–4} Approximately 3% of RCC cases are hereditary, although some hereditary RCC may present without a known family history. Multiple familial RCC syndromes that may confer increased risk of developing RCC have been identified, as have their causative genetic mutations.^{5,6}

Histologic diagnosis of RCC is typically established after surgical removal of renal tumors or after biopsy. Tumor histology, disease stage, and risk stratification of patients is important in therapy selection. Analysis of the SEER database indicates that RCC incidence has been stable and death rates have been declining on average 0.9% each year from 2007 through 2016.⁷ Approximately 75% of people with kidney cancer survive ≥5 years after diagnosis. Prognosis varies widely according to stage at diagnosis. Patients initially diagnosed with clinically localized RCC that is confined to the primary site have a higher 5-year survival (92.5%), largely as a result of surgical

interventions, compared with patients initially diagnosed with distant cancer that has metastasized, among which only 12% survive 5 years.⁷

Regardless of tumor histology, treatment of patients with nonmetastatic primary RCC typically consists of surgery (ie, nephrectomy). Systemic therapy options for patients with relapsed or stage IV disease include kinase inhibitors, mTOR inhibitors, and monoclonal antibodies against VEGF, PD-1, or PD-L1. Recommended systemic therapy regimens vary by patient risk status and tumor histology.

These NCCN Guidelines Insights focus on recent changes to systemic therapy recommendations for relapsed or stage IV RCC with clear cell or nonclear cell histology. Combination axitinib/pembrolizumab was added to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Kidney Cancer in version 4.2019 for treating relapsed or stage IV ccRCC in a second-line or higher setting (see KID-C page 1 of 2, above), whereas combination lenvatinib/everolimus was re-stratified in version 1.2021 according to the NCCN Categories of Preference for treating relapsed or stage IV nonclear cell RCC (nccRCC; see KID-C page 2 of 2, page 1163). This article also discusses newly added information about 7 of the most common hereditary RCC syndromes, as

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY ^g		
Preferred regimens	Other recommended regimens	Useful in certain circumstances
<ul style="list-style-type: none"> • Clinical trial • Sunitinib 	<ul style="list-style-type: none"> • Cabozantinib • Everolimus • Lenvatinib + everolimus 	<ul style="list-style-type: none"> • Axitinib • Bevacizumab^f • Erlotinib • Nivolumab^b • Pazopanib • Bevacizumab^f + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC) • Bevacizumab^f + everolimus • Temsirolimus^e (category 1 for poor-prognosis risk group; category 2A for other risk groups)

^b See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

^e The poor risk model used in the global ARCC trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin <LLN, corrected calcium >10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271–2281.

^f An FDA-approved biosimilar is an appropriate substitution for bevacizumab.

^g For collecting duct or medullary subtypes, partial responses have been observed with cytotoxic chemotherapy (carboplatin + gemcitabine, carboplatin + paclitaxel, or cisplatin + gemcitabine) and other platinum-based chemotherapies currently used for urothelial carcinomas. Gemcitabine + doxorubicin can also produce responses in renal medullary carcinoma (Roubaud G, et al. Oncology 2011;80:214–218; Shah AY, et al. BJU Int 2017;120:782–792). Oral targeted therapies generally do not produce responses in patients with renal medullary carcinoma. Outside of clinical trials, platinum-based chemotherapy regimens should be the preferred therapy for renal medullary carcinoma.

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KID-C
2 of 2

well as genetic risk assessment, testing, surveillance, and treatment recommendations for patients who are suspected or confirmed to have one of these syndromes (see HRCC-1, HRCC-2, GENE-1, HRCC-B page 1 of 2, HRCC-C page 1 of 2, and HRCC-D, pages 1164–1169, respectively).

NCCN Categories of Preference

Starting with version 1.2019, the panel assigned a Category of Preference to all systemic therapy regimens included in the NCCN Guidelines for Kidney Cancer. The 3 NCCN Categories of Preference are as follows:

- Preferred: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability
- Other recommended: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes
- Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation)

The Categories of Preference provide increased granularity and specificity of recommended regimens, and

supplement information provided by the NCCN Categories of Evidence and Consensus (ie, categories 1, 2A, 2B, and 3).

Systemic Therapy Regimens for Relapsed or Stage IV Disease

Combination Axitinib/Pembrolizumab for ccRCC in a Second-Line or Higher Setting

In April 2019, the FDA approved pembrolizumab in combination with axitinib for first-line treatment of patients with advanced RCC.^{8,9} Data from the KEYNOTE-426 trial, which included 861 patients, supported the combination therapy's approval for this indication.¹⁰ In an interim version 4.2019 guidelines update, the panel added axitinib/pembrolizumab as a preferred first-line therapy option for patients in both the favorable and poor/intermediate International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups. For the same update, the panel also discussed whether axitinib/pembrolizumab might be used in clinical practice as an off-label second-line treatment option in patients with relapsed or stage IV ccRCC. Although the panel conceded that there were no published data to support the use of axitinib/pembrolizumab in a second-line setting,

CRITERIA FOR FURTHER GENETIC RISK EVALUATION FOR HEREDITARY RCC SYNDROMES^a

^a Table adapted from ACMG Practice Guidelines. Hampel H, Bennett RL, Buchanan A, et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. *Genet Med* 2015;17:70-87. Schuch B, Vourganti S, Ricketts CJ, et al. Defining early-onset kidney cancer: Implications for germline and somatic mutation testing and clinical management. *J Clin Oncol* 2014;32:431-437.

^b Close blood relatives include the patient's first-degree (ie, parents, siblings, children) and second-degree (ie, half-siblings, aunts, uncles, nieces, nephews, grandparents, grandchildren) relatives.

^c Tumors that show loss of staining for SDHB have been termed SDH-deficient. Morphology of these tumors may include: solid or focally cystic growth, uniform cytology with eosinophilic flocculent cytoplasm, intracytoplasmic vacuolations and inclusions, and round to oval low-grade nuclei. (Ricketts CJ, Shuch B, Vocke CD, et al. Succinate dehydrogenase kidney cancer: an aggressive example of the Warburg effect in cancer. *J Urol* 2012;188:2063-71; Gill AJ, Hes O, Papatomas T, et al. Succinate dehydrogenase [SDH]-deficient renal carcinoma: a morphologically distinct entity: a clinicopathologic series of 36 tumors from 27 patients. *Am J Surg Pathol* 2014;38:1588-1602; Gill AJ. Succinate dehydrogenase [SDH] and mitochondrial driven neoplasia. *Pathology* 2012;44:285-292.)

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HRCC-1

they thought that clinicians were likely to consider the combination therapy as a treatment option in patients with advanced ccRCC whose disease progressed after first-line sunitinib therapy. Thus, they unanimously agreed to add axitinib/pembrolizumab as an “other recommended” option for second-line or higher treatment of relapsed or stage IV ccRCC (see KID-C page 1 of 2, page 1162). The panel gave the combination therapy a category 2A rating because there were no published data to support this recommendation, but noted that they would need to revisit the rating if data on axitinib/pembrolizumab's use in a second-line or higher setting became available.

Combination Lenvatinib/Everolimus for Relapsed or Stage IV nccRCC

In May 2016, the FDA approved lenvatinib, a multitarget kinase inhibitor, in combination with everolimus, an mTOR inhibitor, for treating advanced RCC following one prior antiangiogenic therapy.^{11,12} Data from a randomized phase II trial¹³ partially supported the combination therapy's approval for this indication. The trial enrolled patients with advanced or metastatic ccRCC whose disease had progressed after treatment with a VEGF-targeted

therapy. Based on these data, in version 3.2016, the panel added lenvatinib/everolimus as a category 2A recommendation for treating relapsed or stage IV ccRCC in a second-line or higher setting.

For patients with relapsed or stage IV nccRCC, the benefit of targeted therapy is generally less clear.¹⁴ Although the panel recommends enrollment in a clinical trial as a preferred option for these patients, they have established that certain systemic therapy options recommended for patients with ccRCC may also have some efficacy in those with nccRCC, even in the absence of clinical trial data. Despite the fact that the aforementioned lenvatinib/everolimus trial¹³ only enrolled patients with ccRCC, the panel discussed whether the combination therapy might also be appropriate for use in patients with nccRCC. In version 1.2017, they added lenvatinib/everolimus as a category 2A recommendation for patients with relapsed or stage IV nccRCC. In version 1.2019, when Categories of Preference were added to the NCCN Guidelines for Kidney Cancer, the panel categorized lenvatinib/everolimus as “useful under certain circumstances” systemic therapy regimen for patients with relapsed or stage IV nccRCC; its category 2A recommendation did not change.

HEREDITARY RCC SYNDROMES OVERVIEW

Syndrome/Gene	Histology	Inheritance Pattern Major Clinical Manifestations	Other Specialists Involved in Screening
von Hippel-Lindau (VHL)/ <i>VHL</i> gene	Clear cell	<ul style="list-style-type: none"> Autosomal dominant See Table 2 	<ul style="list-style-type: none"> Neurosurgery Ophthalmology Audiology Endocrinology Endocrine surgery
Hereditary papillary renal carcinoma (HPRC)/ <i>MET</i> gene	Type 1 papillary	<ul style="list-style-type: none"> Autosomal dominant Multifocal, bilateral renal cell tumors 	<ul style="list-style-type: none"> Nephrology
Birt-Hogg-Dubé syndrome (BHDS)/ <i>FLCN</i> gene ^{d,e}	Chromophobe, hybrid oncocytoma	<ul style="list-style-type: none"> Autosomal dominant Cutaneous fibrofolliculoma or trichodiscoma, pulmonary cysts, and spontaneous pneumothorax 	<ul style="list-style-type: none"> Pulmonology Dermatology
Tuberous sclerosis complex (TSC)/ <i>TSC1</i> , <i>TSC2</i> genes	Angiomyolipoma, clear cell	<ul style="list-style-type: none"> Autosomal dominant See Table 1 	<ul style="list-style-type: none"> Neurology Dermatology
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)/ <i>FH</i> gene	HLRCC or FH-associated RCC/ type 2 papillary	<ul style="list-style-type: none"> Autosomal dominant Leiomyomas of skin and uterus, unilateral, solitary, and aggressive renal cell tumors. PET-positive adrenal adenomas 	<ul style="list-style-type: none"> Gynecology Dermatology
BAP1 tumor predisposition syndrome (TPDS)/ <i>BAP1</i> gene ^{f,g}	Clear cell, chromophobe	<ul style="list-style-type: none"> Autosomal dominant Melanoma (uveal and cutaneous), kidney cancer, mesothelioma 	<ul style="list-style-type: none"> Dermatology Ophthalmology Thoracic oncology
Hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome/ <i>SDHA/B/C/D</i> genes	Clear cell (not usually <i>SDHB</i>), chromophobe, papillary type 2, renal oncocytoma, oncocytic neoplasm	<ul style="list-style-type: none"> Autosomal dominant Head and neck paraganglioma and adrenal or extra-adrenal pheochromocytomas, benign lung lesions, GIST tumors 	<ul style="list-style-type: none"> Endocrine Endocrine surgery

See GENE-1

^d Schmidt LS, Nickerson ML, Warren MB, et al. Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dubé syndrome. *Am J Hum Genet* 2005;76:1023-1033.

^e Sattler EC, Steinlein OK. Birt-Hogg-Dubé Syndrome. 2006 Feb 27 [Updated 2020 Jan 30]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle;1993-2020.

^f Peña-Llopis S, Vega-Rubín-de-Celis S, Liao A. BAP1 loss defines a new class of renal cell carcinoma. *Nat Genet* 2012;44:751-759.

^g Hakimi AA, Ostrovskaya I, Reva B. Adverse outcomes in clear cell renal cell carcinoma with mutations of 3p21 epigenetic regulators BAP1 and SETD2: a report by MSKCC and the KIRC TCGA Research Network. *Clin Cancer Res* 2013;19:3259-3267.

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HRCC-2

When considering updates to version 1.2021 of the guidelines, the panel reviewed newly available conference abstract data¹⁵ from an ongoing single-arm phase II trial (ie, ClinicalTrials.gov identifier: NCT02915783) enrolling 31 patients with unresectable advanced or metastatic nccRCC who had not previously received chemotherapy. All patients in the trial received combination lenvatinib/everolimus. The investigators reported an objective response rate (ORR) of 25.8% (95% CI, 11.9%–44.6%); 8 patients in the trial achieved a partial response (PR; papillary, n=3; chromophobe, n=4; unclassified, n=1) and none had a complete response (CR). At the time of data reporting, the median duration of response was not reached. A total of 18 patients (58.1%) had stable disease (SD), and the clinical benefit rate (CR + PR + durable SD [duration ≥23 weeks]) was 61.3% (95% CI, 42.2%–78.2%). Median progression-free survival was 9.23 months (95% CI, 5.49–not estimable [NE]) and median overall survival was 15.64 months (95% CI, 9.23–NE).

Although the panel conceded that these data had not yet been published and that the number of enrolled patients was small, they generally felt that lenvatinib/everolimus treatment led to improved patient outcomes

across all nccRCC subtypes. Thus, the overwhelming majority agreed to reclassify lenvatinib/everolimus as an “other recommended” systemic therapy regimen for patients with nccRCC; the Category of Evidence and Consensus rating remained as 2A (see KID-C page 2 of 2, page 1163).

Hereditary RCC Syndromes: Clinical Features, Genetic Testing, and Surveillance

Although hereditary RCC is relatively rare (~3% of all cases),⁵ the panel felt that it was important to provide recommendations for patients with a suspected or confirmed hereditary RCC syndrome, and thus established a subcommittee of panel members to develop a new section on hereditary RCC. Accordingly, version 1.2021 of the NCCN Guidelines for Kidney Cancer describes 7 of the most common hereditary RCC syndromes that may predispose patients to RCC: *BAP1* tumor predisposition syndrome (*BAP1*-TPDS), Birt-Hogg-Dubé syndrome (BHDS), hereditary leiomyomatosis and renal cell cancer (HLRCC), hereditary papillary renal carcinoma (HPRC), hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC), tuberous sclerosis (TSC), and Von Hippel-Lindau (VHL) disease.

^a In individuals who meet diagnostic criteria, but in whom no germline mutations are identified, consider workup for mosaicism.

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GENE-1

The guidelines describe kidney-specific clinical features and manifestations of each of these syndromes and known associated genes/inheritance patterns, and provide genetic testing, surveillance, and treatment recommendations for patients who are suspected or confirmed to have a hereditary RCC syndrome. Although published data informed most of these recommendations, the panel also relied on the real-world experience and expertise of the hereditary subcommittee to develop recommendations in instances of limited data.

While discussing the potential scope and content of this new section, the subcommittee noted that there are some syndromes associated with RCC that overlap with other cancers (eg, Cowden syndrome, Lynch syndrome). For Cowden and Lynch syndromes, the panel refers readers to the information provided in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and Genetic/Familial High-Risk Assessment: Colorectal, respectively (available at NCCN.org). Future versions of the guidelines may be expanded to include other hereditary syndromes, such as microphthalmia-associated transcription factor (MITF)-related cancer syndrome, which predisposes patients to melanoma and/or RCC.⁶

The subcommittee also noted that patients with hereditary RCC syndromes often experience nonrenal manifestations, but they felt that input from clinicians from other specialties (eg, dermatology, endocrinology, neurology, ophthalmology, urology) would be necessary to provide consensus-based recommendations for all potential manifestations. Accordingly, they limited the scope of this new section in version 1.2021 to only include kidney-specific clinical features and manifestations, but identified specialists who may be helpful in managing nonrenal manifestations in patients with a hereditary RCC syndrome (see HRCC-2, page 1165).

Recommendations for genetic testing, surveillance, and treatment vary according to the patient's personal and/or family history of a hereditary RCC syndrome or clinical diagnosis of RCC. Following is a summary of recommendations by patient population and the panel's rationale for these recommendations.

Recommendations for Patients With a Personal or Family History of an RCC Syndrome

The panel recommends that patients with a personal or family history of an RCC syndrome who have not

KIDNEY-SPECIFIC SCREENING RECOMMENDATIONS FOR PATIENTS WITH CONFIRMED HEREDITARY RCC
WHO DO NOT YET HAVE A RADIOGRAPHIC OR PATHOLOGIC DIAGNOSIS OF RCC

General

- Follow-up should be individualized based on treatment schedules, side effects, comorbidities, and symptoms.
- Whenever possible, screening should be coordinated with other specialist involved in patient's care.
- Women of childbearing age who are planning conception should consider renal imaging prior to pregnancy.
- If there is a family member with an early diagnosis, screening should begin 10 y before earliest age of diagnosis in family member.
- CT of the abdomen can be used for surgical planning but should be limited if possible for surveillance due to lifetime radiation exposure for hereditary syndromic patients.
- Imaging frequency would be increased once lesions are detected based on growth rate and size of lesion(s).
- For surgical recommendations for each syndrome, see [HRCC-C](#); for systemic therapy, see [HRCC-D](#).

BAP1-TPDS

- Abdominal MRI (preferred) or CT with and without IV contrast every 2 y starting at age 30 y¹

BHDS

- Abdominal MRI (preferred) or CT with and without IV contrast every 3 y starting at age 20 y²

HLRCC

- Abdominal MRI (preferred) or CT with and without IV contrast annually starting at age 8–10 y³

HPRC

- Abdominal MRI (preferred) or CT with and without IV contrast every 1–2 y starting at age 30 y^{4,5}

PGL/PCC

- Abdominal MRI (preferred) or CT with and without IV contrast every 4–6 y starting at age 12 y^{5,6,8}

TSC

- Abdominal MRI (preferred) or CT with and without IV contrast every 3–5 y starting at age 12 y⁷

VHL

- Abdominal MRI (preferred) or CT with and without IV contrast to assess kidneys, pancreas, and adrenals every 2 y starting at age 15 y⁵

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HRCC-B
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yet been diagnosed with RCC should undergo genetic evaluation (see HRCC-1, page 1164). If patients harbor a pathogenic or likely pathogenic genetic mutation associated with an RCC syndrome, they should undergo screening for the development of RCC.

For screening in patients who are confirmed to have a hereditary RCC syndrome, the panel recommends use of MRI (preferred). CT may also be used for surgical planning purposes, but the panel warns that use of abdominal CT should be limited due to the potential of increased lifetime radiation exposure. The panel also includes recommendations on testing intervals and the age at which patients should begin regular screening, because both vary widely by the hereditary RCC syndrome in question. Although patients with HLRCC should undergo imaging annually,¹⁶ those with less aggressive syndromes such as PGL/PCC may benefit from testing at longer intervals.^{17–19} For a detailed list of these recommendations, see HRCC-B page 1 of 2 (above).

The age at which patients should begin screening also varies by hereditary RCC syndrome (see HRCC-B page 1 of 2, above). Thus, the panel recommends that patients with confirmed HLRCC, PGL/PCC, TSC,

and VHL disease begin screening in childhood.^{16–20} In contrast, those with *BAP1*-TPDS, BHDS, or HPRC should begin screening in adulthood (ie, age 20 years for BHDS, age 30 years for *BAP1*-TPDS and HPRC).^{17,21–23} However, the panel notes that if a patient has a known family member with an early diagnosis of hereditary RCC, screening should begin 10 years before the age that the family member was diagnosed, regardless of the syndrome in question.

Recommendations for Patients With RCC Who Have Characteristics Consistent With Inherited RCC

Although most of the new hereditary RCC section in version 1.2021 of the guidelines focuses on patients who have not yet been clinically diagnosed with RCC, the panel felt that they should also include recommendations for patients who already have a clinical or pathologic diagnosis of RCC and have characteristics potentially associated with a hereditary syndrome (eg, RCC diagnosis at ≤ 46 years of age, presence of bilateral or multifocal tumors, and/or ≥ 1 known first- or second-degree relative with RCC). These patients should also undergo genetic risk assessment and, if indicated,

KIDNEY-SPECIFIC SURGICAL RECOMMENDATIONS FOR PATIENTS WITH CONFIRMED HEREDITARY RCC

- Preoperative alert: Patients with a suspected or known diagnosis of PGL/PCC or VHL are at increased risk of pheochromocytomas and should have blood and/or urine screening for this prior to any surgical procedure.

BAP1-TPDS

- No specific guidelines in surgical management for this syndrome (See KID-A).

BHDS

- Nephron-sparing surgery is the treatment of choice for renal tumors whenever possible, with consideration that an individual may have multiple tumors during their lifetime.¹
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

HLRCC

- As these tumors can be aggressive, surveillance of renal tumors is not recommended, and total radical nephrectomy should be considered.²

HPRC

- Nephron-sparing surgery is the treatment of choice for renal tumors whenever possible, with consideration that an individual may have multiple tumors during their lifetime.
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

PGL/PCC

- Malignant tumors absent aggressive histology and early stage should undergo surgical resection; partial nephrectomy can be considered.
- For larger tumors and those with aggressive histology (eg, high grade, sarcomatoid), radical nephrectomy should be considered.³

TSC

- AML is a benign lesion associated with TSC and managed separately.^{4,5,6}
- Nephron-sparing surgery is the treatment of choice for malignant renal tumors whenever possible, with consideration that an individual may have multiple tumors during their lifetime.⁷
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

VHL

- Management of localized renal masses in patients with VHL are typically guided under the “3 cm rule.”⁷
- The idea is to intervene at a time point of maximal benefit to the patient to limit the chance of development of metastatic disease but also to consider the recurrent and multiple resections many of these patients will have over the course of their lifetime with subsequent development of chronic and progressive renal failure.^{7,8}
- Patient should undergo partial nephrectomy if at all possible and consider referral to centers with surgical expertise in complex partial nephrectomies and management of VHL patients.⁸
- Ablative treatment options may be considered for those with significant medical or surgical risk to undergo an operation.

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genetic testing. If inherited RCC is confirmed, patients should undergo screening as described earlier, in addition to disease stage-appropriate surveillance (see GENE-1, page 1166).

Surgical Recommendations for Patients With a Confirmed Hereditary RCC Syndrome

The panel also provides surgical recommendations for most of the included hereditary RCC syndromes (see HRCC-C page 1 of 2, above), which are based on published data and/or the subcommittee's real-world experience in treating patients with these syndromes. To develop these recommendations, they carefully weighed the potential morbidity and mortality of surgical treatment against the potential aggressiveness of each of the syndromes. They agreed that patients with BHDS, HPRC, and TSC may benefit from more conservative treatment, such as nephron-sparing surgery or ablative therapies,^{24,25} whereas patients with HLRCC should undergo total radical nephrectomy.¹⁶ The panel's recommendations for surgical treatment of PGL/PCC vary by tumor size and histology: those with smaller, less-aggressive tumors may be eligible for partial nephrectomy, whereas those

with larger, more-aggressive tumors (eg, high-grade, sarcomatoid) should undergo radical nephrectomy.²⁶ Tumor size also factored into the panel's surgical recommendations for patients with VHL disease; they noted that these patients are likely to undergo multiple surgical resections during their lifetime that may contribute to chronic and progressive renal failure. Thus, the timing of surgical intervention must be carefully determined to limit both the development of metastases and morbidity associated with surgical intervention. They agreed that only patients with VHL disease with tumors approaching 3 cm in diameter should undergo partial nephrectomy (or ablative therapy if nephrectomy is contraindicated).^{25,27}

Systemic Therapy for Patients With a Confirmed Hereditary RCC Syndrome

Version 1.2021 of the guidelines includes a limited number of kidney-specific systemic therapy options for patients with hereditary RCC (see HRCC-D, page 1169). While discussing potential content for this new section, the panel noted a lack of FDA-approved systemic therapy regimens for most of the included

KIDNEY-SPECIFIC SYSTEMIC THERAPY FOR PATIENTS WITH CONFIRMED HEREDITARY RCC

HLRCC

- There are no specific FDA-approved therapies for HLRCC. Treatment with erlotinib plus bevacizumab¹ demonstrated benefit in patients with metastatic RCC from HLRCC (See KID-C).²

TSC

- Everolimus is an FDA-approved therapy for asymptomatic, growing angiomyolipoma measuring >3 cm in diameter.³

VHL Disease

- At this time there are no FDA-approved therapies for nonmetastatic RCC arising in VHL disease. However, pazopanib was associated with a >50 % objective response rate in renal lesions in a 31-patient phase II study.⁴

¹ An FDA-approved biosimilar is an appropriate substitution for bevacizumab.

² Srinivasan R, Su D, Stamatakis L, et al. Mechanism based targeted therapy for hereditary leiomyomatosis and renal cell cancer (HLRCC) and sporadic papillary renal cell carcinoma: interim results from a phase 2 study of bevacizumab and erlotinib [abstract]. Eur J Cancer 2014;Abstract 50.

³ Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2013;381:817-824.

⁴ Jonasch E, McCutcheon IE, Gombos DS, et al. Pazopanib in patients with von Hippel-Lindau disease: a single-arm, single-centre, phase 2 trial. Lancet Oncol 2018;19:1351-1359.

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HRCC-D

hereditary RCC syndromes. Among the included hereditary RCC syndromes, only TSC has an FDA-approved systemic therapy regimen: the mTOR inhibitor everolimus was approved in April 2012 for treating TSC-associated benign renal angiomyolipomas not requiring immediate surgery.^{28,29}

The panel also included erlotinib/bevacizumab for patients with HLRCC-associated metastatic RCC and pazopanib for those with VHL disease-associated non-metastatic lesions. Although these systemic therapy regimens are not FDA-approved for use in these patient populations, their inclusion is supported by clinical trial data showing improved patient outcomes. Erlotinib/bevacizumab treatment led to a 60% ORR and a median progression-free survival of 24.2 months in 20 patients with HLRCC-associated RCC,³⁰ whereas pazopanib led to a 42% ORR and a 52% renal tumor-specific response rate in 31 patients with VHL disease.³¹ It is important to note that the panel's inclusion of these 3 systemic therapy regimens does not constitute an official recommendation for their use. Future versions of the guidelines could contain additional systemic therapy options and/or recommendations for patients with hereditary RCC, pending the availability of additional

FDA-approved regimens and/or data supporting off-label use of existing regimens approved for treating RCC.

Conclusions

Emerging evidence informs panel recommendations in the NCCN Guidelines for Kidney Cancer and all other NCCN Guidelines. However, some treatment recommendations may also be informed by real-world clinical practice use and applicability in the absence of published data. Recent updates to the NCCN Guidelines for Kidney Cancer include new and restratified treatment option recommendations that may provide safer and more effective care for patients with kidney cancer. The panel also recently added new information on 7 of the most common hereditary RCC syndromes, and provides recommendations for genetic testing, screening, and/or treatment in patients who are suspected or confirmed to have one of these syndromes. This new section may help clinicians more effectively diagnose and manage patients with hereditary RCC, which is a complex and heterogeneous disease.

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