Original Article

Genetic Risk Assessment for Hereditary Renal Cell Carcinoma: Clinical Consensus Statement

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BACKGROUND: Although renal cell carcinoma (RCC) is believed to have a strong hereditary component, there is a paucity of published guidelines for genetic risk assessment. A panel of experts was convened to gauge current opinions. **METHODS:** A North American multidisciplinary panel with expertise in hereditary RCC, including urologists, medical oncologists, clinical geneticists, genetic counselors, and patient advocates, was convened. Before the summit, a modified Delphi methodology was used to generate, review, and curate a set of consensus questions regarding RCC genetic risk assessment. Uniform consensus was defined as ≥85% agreement on particular questions. **RESULTS:** Thirty-three panelists, including urologists (n = 13), medical oncologists (n = 12), genetic counselors and clinical geneticists (n = 6), and patient advocates (n = 2), reviewed 53 curated consensus questions. Uniform consensus was achieved on 30 statements in specific areas that addressed for whom, what, when, and how genetic testing should be performed. Topics of consensus included the family history criteria, which should trigger further assessment, the need for risk assessment in those with bilateral or multifocal disease and/or specific histology, the utility of multigene panel testing, and acceptance of clinician-based counseling and testing by those who have experience with hereditary RCC. **CONCLUSIONS:** In the first ever consensus panel on RCC genetic risk assessment, 30 consensus statements were reached. Areas that require further research and discussion were also identified, with a second future meeting planned. This consensus statement may provide further guidance for clinicians when considering RCC genetic risk assessment. ***Cancer* 2021;127:3957-3966**. *© 2021 American Cancer Society.*

LAY SUMMARY:

- The contribution of germline genetics to the development of renal cell carcinoma (RCC) has long been recognized.
- However, there is a paucity of guidelines to define how and when genetic risk assessment should be performed for patients with known or suspected hereditary RCC.
- Without guidelines, clinicians struggle to define who requires further evaluation, when risk assessment or testing should be done, which genes should be considered, and how counseling and/or testing should be performed.
- To this end, a multidisciplinary panel of national experts was convened to gauge current opinion on genetic risk assessment in RCC and to enumerate a set of recommendations to guide clinicians when evaluating individuals with suspected hereditary kidney cancer.

KEYWORDS: clinical consensus, genetic risk assessment, genetic testing, germline mutations, hereditary kidney cancer, recommendations, renal cell carcinoma.

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INTRODUCTION

Cancers of the kidney and renal pelvis accounted for an estimated 73,820 new cancer diagnoses and 14,770 deaths in the United States in 2019, and renal cell carcinoma (RCC) is the most common manifestation.[1] It has long been postulated that from 2% to 8% of RCCs have a hereditary component; however, the proportion of these that are associated with an alteration in a single gene is unknown.[2,3] Classic hereditary RCC syndromes, such as von Hippel-Lindau (VHL) disease, are highly penetrant, with associated clinical manifestations that are rarely seen sporadically. However, newer RCC syndromes may have lower penetrance and fewer associated clinical manifestations. The Cancer Genome Atlas analysis and recent institutional series of patients with advanced kidney cancer identified germline mutations in known cancer-associated genes in 6% to 16% of submitted RCCs,[4] including mutations not previously believed linked to RCC.[5] There are now 15 genes with characterized alterations that are associated with RCC.[6,7] However, family registry data and twin studies suggest additional mechanisms of inherited susceptibility to developing RCC, such as autosomal recessive factors and single nucleotide variants.[8]

To assess an individual's genetic risk, detailed personal and family histories are considered essential elements of an initial evaluation, which can be further augmented by a comprehensive physical examination by clinical providers. However, many specialists may perform a more focused evaluation and may miss subtle clues suggestive of a hereditary cancer syndrome. A more comprehensive evaluation may be performed by individuals who have advanced training in genetic risk assessment. When medically indicated and fully informed of the risks and benefits, patients may decide whether to pursue further genetic testing. Germline testing has dramatically evolved in RCC over the past 2 decades, with significantly reduced costs, more rapid turnaround time, and a higher number of genes on specific next-generation sequencing panels.[9]

However, despite the availability of both tests and providers, our current clinical guidelines on the specifics of RCC genetic risk assessment are lacking. Without clear guidelines, clinicians struggle to define who requires further evaluation, when risk assessment or testing should be done, which genes should be considered, and how counseling and/or testing should be performed. The lack of a strong consensus has also led insurance companies to adopt various policies on coverage for germline testing, making it difficult for some patients to have access to appropriate care. To develop a working set of clinical recommendations for genetic testing for patients who have a diagnosis of or are at risk for RCC, a panel of experts was convened to assess current thoughts on genetic risk assessment in RCC with the goal of developing clinical consensus statements.

MATERIALS AND METHODS

Expert Panel

Before the inaugural 2019 Kidney Cancer Research Summit, jointly sponsored by KidneyCAN (Philadelphia, Pennsylvania) and the Department of Defense Kidney Cancer Research Program, a multidisciplinary group of national experts was invited to participate in a consensus panel and round-table discussion. Members from every VHL Alliance Comprehensive Care Center as well as individuals attending the Kidney Cancer Research Summit who had relevant publications and/or expertise in hereditary RCC were invited. In addition, leading RCC patient advocates were invited to participate and provide a patient perspective. An initial questionnaire assessed specialty, experience, and practice patterns.

Modified Delphi Methodology

To generate a consensus on the current state of the field, we structured a series of questions following the Delphi consensus methodology, a now commonly used technique to address gaps in patient care and facilitate consensus development in evidence-based medicine.[7,8] Before the meeting, feedback on knowledge gaps and specific questions were solicited from all invited guests. The questions were independently reviewed by a steering committee consisting of members of the panel and co-chairs. The questions were discussed over several conference calls to consolidate, format, and group into thematic categories. The resultant questionnaire was transcribed to an electronic polling system (see Supporting Table 1).

Consensus Meeting

The meeting was held on September 12, 2019 in Philadelphia. Before administration of the questionnaire, there was a brief presentation session summarizing the known genetic conditions, the state of genetic testing, available panels, and ongoing issues and controversies in genetic risk assessment. With all invitees in attendance, questions were projected on the screen, and responses were recorded anonymously using the audience response system. After ≥90% of participants responded to each question, the results of the voting were revealed to the group immediately to allow for brief discussion. Controversial topics were revisited at the end of the polling session, and questions were revised where ambiguity

TABLE 1. Pooled Participant Specialties and Practice Information

Variable	No. (%)
Specialty	
Urology	13 (39)
Medical oncology	12 (36)
Genetic counselor	4 (12)
Clinical geneticist	2 (6)
Patient advocate	2 (6)
Years in practice	
Average	13.1 ± 9.6
How many patients do you recommend for kidney cancer genetic risk assessment annually?	
<10	2 (6)
10-20	6 (20)
20-50	12 (40)
>50	6 (20)
Do you order your own testing?	
Yes	19 (63)
No	7 (23)
How often have your patients had trouble with insurance reimbursement for genetic testing?	
0%	4 (13)
0%-20%	9 (30)
20%-50%	8 (27)
>50%	2 (7)

was present. The level of consensus was defined in accordance with National Comprehensive Cancer Network (NCCN) criteria, which defines *uniform consensus* as ≥85% agreement, and *general consensus* as ≥50% agreement.[10] Because most of the questions had a binary outcome, only the uniform consensus was emphasized as reaching a *consensus* agreement. Questions with >50% agreement were also discussed in detail when moderators deemed them highly relevant and with direct impact to clinical practice. All available submitted responses by participating panelist were summarized.

RESULTS

After invited questions were received and curated by the steering committee, in total, 53 questions were included for panel review. These questions were grouped into 5 categories: 1) *who* should undergo genetic risk assessment, 2) *when* should genetic risk assessment be performed, 3) *what* testing should be performed, 4) *how* should germline risk assessment be conducted, and 5) testing in cases of isolated extrarenal lesions associated with known syndromes. The results of the initial demographic and practice pattern questionnaire are detailed in Table 1. Attendance included 33 panelists with significant clinical expertise in the field of hereditary RCC and RCC patient advocates. The panel included representation from urologists (n = 13), medical oncologists (n = 12), genetic counselors and clinical geneticists (n = 6), and patient advocates (n = 2) (see Supporting Table 2).

TABLE 2. Who Should Undergo Genetic Risk Assessment?

Consensus Question	Yes, %	No, %
Should an individual with renal tumors and syndromic manifestations associated with hereditary kidney cancer be offered genetic risk assessment?	100[a]	0
Should an individual without renal tumors and syndromic manifestations associated with hereditary kidney cancer be offered genetic risk assessment?	100[a]	0
Should an individual with renal tumors and a first degree family member with syndromic manifestations (pheochromocytoma, melanoma, pneumothorax) associated with hereditary kidney cancer be offered genetic risk assessment?	96[a]	4
Should an individual without renal tumors and a first-degree family member with worrisome syndromic manifestations (pheochromocytoma, melanoma, pneumothorax) associated with hereditary kidney cancer be offered genetic risk assessment?	95[a]	5
For an individual with or without renal tumor(s) but first-degree relatives with documented germline mutation associated with RCC, should genetic risk assessment be offered?	100[a]	0
For an individual with or without renal tumor(s) but a second-degree family member with documented germline mutation associated with RCC, should genetic risk assessment be offered before testing the first-degree relative?	53	47
For an individual with or without renal tumor(s) but second-degree relatives with documented germline mutation associated with RCC and inability to test first-degree relatives, should genetic risk assessment be offered?	90[a]	10
For an individual with a renal tumor(s) and a first-degree relative with RCC, should genetic risk assessment be offered?	90[a]	10
For an individual with a renal tumor(s) and 2 second-degree relatives (same lineage) with RCC, should genetic risk assessment be offered?	87[a]	13
For an individual with a renal tumor(s) and 1 second-degree relative with RCC with unknown histology, should genetic risk assessment be offered?	20	80
For an individual without a renal tumor(s) and first-degree relative(s) with RCC, should genetic risk assessment be offered?	23	77
For an individual without a renal tumor(s) and 1 second-degree relative with RCC, should genetic risk assessment be offered?	11	89[a]
In the absence of syndromic manifestations, should individuals with bilateral or multifocal renal tumors be offered genetic risk assessment?	93[a]	7
Are there specific renal tumor histologies that should lead to recommendations for genetic risk assessment?	97[a]	3
Is needle biopsy (without resected pathology) sufficient to pursue genetic risk assessment?	73	27
For individuals with histology suggestive of an SDH renal tumor, should genetic risk assessment be offered?	100[a]	0
For individuals with histology suggestive of an FH-deficient renal tumor, should genetic risk assessment be offered?	100[a]	0
For individuals with histology suggestive of a hybrid renal tumor (oncocytoma and chromophobe), should genetic risk assessment be offered?	86[a]	14
Should those with bilateral or multifocal chromophobe RCC be recommended for genetic risk assessment?	93[a]	7

(*Continued*)

TABLE 2. *Continued*

Consensus Question	Yes, %	No, %
Should those with bilateral or multifocal papillary type 1 RCC be recommended for genetic risk assessment?	85[a]	15
Should those with bilateral or multifocal clear cell RCC be recommended for genetic risk assessment?	93[a]	7
Should those with bilateral or multifocal renal angiomyolipomas be recommended for genetic risk assessment?	86[a]	14
Should age be a sole criterion for genetic risk assessment?	70	30
If an age cutoff was recommended for genetic risk assessment based on SEER age distributions, what age do you feel this should be?		
1) 54 y (25th percentile)	17	
2) 46 y (10th percentile)%	67	
3) 40 y (5th percentile)	7	
4) 36 y (2.5th percentile)	10	

Abbreviations: FH Fumarate hydratase; RCC, renal cell carcinoma; SDH, succinate dehydrogenase; SEER, Surveillance, Epidemiology, and End Results program of the National Cancer Institute.
[a]These statements represent those that reached a consensus.

Who Should Undergo Genetic Risk Assessment?

Twenty-four questions addressing *who* should undergo genetic risk assessment were reviewed (Table 2). Panelists reached uniform consensus for 18 (75%) questions. There was general agreement on the management of individuals with a personal or family history of classic syndromic manifestations associated with hereditary RCC, such as pheochromocytoma, melanoma, or spontaneous pneumothorax. This included assessment of those individuals with or without RCC who personally exhibited syndromic manifestations and those with or without RCC who had family members with syndromic manifestations. It was agreed that further genetic risk assessment should be performed for an individual who has a first-degree or second-degree relative (if no first-degree relative is available) with a documented germline mutation.

In discussing what constitutes a *strong* family history requiring further assessment, it was agreed that an individual with a renal tumor who has a first-degree relative or 2 second-degree (same lineage) relatives with RCC should undergo targeted genetic risk assessment. There was no consensus on testing unaffected individuals who have first-degree relatives with RCC; however, it was agreed that having 1 affected second-degree relative was not sufficient to recommend further genetic risk assessment.

The panel also achieved uniform consensus that specific RCC histology should prompt further evaluation, including various nonclear cell RCC histologies suggestive of succinate dehydrogenase (SDH)-deficient tumors, fumarate hydratase (FH)-deficient tumors, or hybrid oncocytic renal tumors. There was uniform consensus that patients with bilateral or multifocal renal tumors should be offered genetic risk assessment, although there was a discussion that many of these patients, especially older individuals (aged >60 years), would likely not require further testing or would test negative.

TABLE 3. When Should Genetic Risk Assessment Be Performed?

Consensus Question	Yes, %	No, %
In the absence of syndromic manifestations, should an individual with bilateral or multifocal renal tumors have a histologic diagnosis before genetic risk assessment?	57	43
In the absence of syndromic manifestations, should an individual with a solitary renal tumor with ≥1 hereditary risk factor(s) have a histologic diagnosis before genetic risk assessment?	41	59
In the absence of syndromic manifestations, should an individual with localized, bilateral, or multifocal renal tumors have genetic risk assessment before management?	79	21
In the absence of syndromic manifestations, should an individual with a localized, solitary renal tumor with ≥1 hereditary risk factor(s) have genetic risk assessment before management?	59	41
In an individual with a localized renal lesion <3 cm and strong suspicion for a hereditary cancer syndrome, should genetic risk assessment be performed before management?	93[a]	7
In metastatic disease that doesn't require urgent treatment, when there is concern for hereditary form of RCC, do you think genetic risk assessment should be done before management is initiated?	48	52
In a patient with a renal tumor and skin lesion(s) resembling those associated with a renal cancer syndrome, should a skin biopsy be required to guide genetic risk assessment?	14	86[a]

Abbreviation: RCC, renal cell carcinoma.
[a]These statements represent those that reached a consensus.

The discussion of a cutoff age for genetic risk assessment was highly contentious. Participants believed that the most pressing question was to broadly ask whether age alone was a sufficient criterion to recommend genetic risk assessment in a patient with a renal tumor. Although there was general consensus (70%) on this statement, there was no uniform consensus, as some argued that the overall prevalence of relevant genetic alterations is very low across age strata, whereas others expressed that *age alone* may reliably guide the need for testing. For those supporting further genetic risk assessment based on threshold age, most (67%) agreed on an age cutoff of ≤46 years.

When Should Genetic Risk Assessment Be Initiated?

Seven questions on *when* genetic risk assessment should be initiated were reviewed (Table 3). Panelists reached

TABLE 4. What Type of Genetic Testing Should Be Performed?

Consensus Question	Single-Gene, %	Multigene, %
In general, should individuals with suspicion for a classic syndrome be considered for single-gene or multigene panel testing?	83	17
In general, should individuals without suspicion of a classic syndrome but ≥1 risk factor for hereditary kidney cancer be considered for single-gene or multigene panel testing?	10	90[a]
Consensus Question	**Yes, %**	**No, %**
An individual with kidney cancer undergoes somatic tumor profiling and is found with an alteration in a cancer gene associated with hereditary RCC (not VHL); in the absence of risk factors, should this individual undergo genetic risk assessment?	21	79[b]
If the above individual were to pursue genetic risk assessment for an alteration identified on a somatic panel, should testing consist of a single-gene assay?	97[a]	3
Should a negative somatic tumor profiling report (without germline testing) influence the decision to pursue genetic risk assessment?	39	61

Abbreviations: RCC, renal cell carcinoma; VHL, von Hippel-Lindau disease.
[a]These statements represent those that reached a consensus.
[b]Seventy-nine percent voted that the response to this question depends on the specific gene in question.

uniform consensus on only 2 (28.4%) questions. The panel agreed (93%) that, for individuals with a localized renal lesion <3 cm and a strong suspicion for a hereditary RCC syndrome, genetic risk assessment should be performed before management. In addition, for those with a renal tumor and a suspicious associated skin lesion, there was consensus that a skin biopsy would not be required before genetic risk assessment (86%). There was agreement among most participants (79%) that patients with bilateral or multifocal tumors (without syndromic manifestations) should have genetic risk assessment performed before management, but there was only limited agreement (57%) about the role of histologic diagnosis before initiating genetic risk assessment. Similarly, for individuals with a solitary renal tumor who had ≥1 hereditary risk factor(s), defined as a first-degree relative with RCC, a documented mutation, multifocal disease, or other syndromic manifestations, there was general consensus regarding the need for histologic diagnosis (59%) and providing risk assessment before surgical management (59%).

What Testing Should Be Performed?

Five questions addressed what specific testing should be performed when genetic risk assessment was indicated (Table 4). Panelists reached uniform consensus on only 2 (40%) questions. There was uniform consensus (90%) that an individual without suspicion of a particular syndrome but with risk factors for hereditary kidney cancer should undergo multigene panel testing, rather than single-gene testing. There was general consensus (83%) that individuals suspected of having a particular syndrome (with a defined gene) be considered for single-gene, rather than multigene, panel testing.

When somatic tumor testing had been previously performed and an alteration in a gene associated with a hereditary cancer syndrome was identified, the majority of the panel believed that further genetic evaluation would depend on the particular gene. However, if performed, there was uniform consensus that only a single-gene test should be conducted in the absence of other risk factors. There was general consensus (61%) that, if somatic-only tumor profiling is performed and does not identify an alteration in genes associated with hereditary RCC, this information should not influence germline genetic risk assessment.

How Should Genetic Risk Assessment Be Performed?

Six questions addressed *how* genetic risk assessment should be performed (Table 5), of which 4 (66.7%) had uniform consensus. The panel agreed with uniform consensus that no germline testing should be done without pretest counseling (100%) and that physicians, such as urologists and oncologists with expertise in hereditary kidney cancer syndromes, may themselves offer counseling before genetic testing (92%). Because access to qualified providers may be a barrier to care, there was uniform consensus (93%) that a telehealth visit with a licensed counselor would be sufficient for evaluation. Some (59%) believed that a standardized video covering essential elements of pretest counseling may be sufficient before testing. However, there was significant concern that this may not be sufficient without an opportunity for discussion with

TABLE 5. How Should Germline Risk Assessment Be Performed?

Consensus Question	Yes, %	No, %
Can physicians (urologists/oncologist) with expertise in hereditary kidney cancer syndromes offer *pretest* counseling in patients suspected of having hereditary kidney cancer?	92[a]	8
Is a standardized video covering essential elements of counseling sufficient for *pretest* counseling in individuals suspected of having hereditary kidney cancer?	59	41
Should germline testing in patients who did not have any pre-test counseling be performed?	0	100[a]
If an individualized *pretest* counseling was not performed, but germline testing is pursed, testing should:		
1) Include a comprehensive cancer gene panel to avoid testing too narrowly	8	
2) Include a kidney specific gene panel only to keep focused	92[a]	
Is a telehealth/telegenetics visit with a licensed counselor sufficient for evaluation of individuals suspected of having hereditary kidney cancer?	93[a]	7
Should individuals with variants of unknown significance in genes that could explain a hereditary kidney cancer phenotype be treated as affected until more information is obtained?	56	44

[a]These statements represent those that reached a consensus.

a qualified provider and further refinement of individualized risk. If a nonstandardized approach was taken, there was consensus that a kidney-specific panel (92%) should be pursued to avoid testing too broadly.

A long discussion was held on the topic of variants of unknown significance (VUS) in genes that could explain a hereditary kidney cancer phenotype and their implications for screening and surgical management. Whereas most members (56%) agreed that the presence of hereditary syndromic manifestations with a VUS in the relevant gene raises suspicion for a pathogenic variant, there was strong sentiment that a VUS should be noted but not acted upon and that patients should be managed based on standard clinical criteria.

Testing in Cases of Isolated Extrarenal Manifestations

Eight questions addressed pursuing testing for an isolated extrarenal manifestation associated with known RCC syndromes in the absence of family history (Table 6). Panelists reached uniform consensus for 4 (50%) questions. The panel reached uniform consensus that patients with a pheochromocytoma/paraganglioma (100%), an endolymphatic sac tumor (100%), uveal melanoma (88%), and FH-deficient uterine fibroids (93%) should undergo genetic risk assessment and consideration of genetic testing. Other isolated extrarenal manifestations that did not reach consensus regarding necessitation of genetic testing included an isolated hemangioblastoma (brain, spinal cord, or retina), cutaneous or uterine leiomyomas with unknown *FH* status, spontaneous pneumothorax, and fibrofolliculoma.

TABLE 6. Which Isolated Extrarenal Findings Should Prompt Consideration of Genetic Risk Assessment?

Consensus Question	Yes, %	No, %
Independent of family history, should a patient with the following isolated extrarenal manifestation undergo genetic testing?		
A single hemangioblastoma (CNS and/or retina)	48	52
A single pheochromocytoma or paraganglioma	100[a]	0
A single endolymphatic sac tumor	100[a]	0
A single cutaneous leiomyoma	57	43
A history of spontaneous pneumothorax	32	68
Skin fibrofolliculomas	56	44
Uveal melanoma	88[a]	12
A single FH-deficient uterine fibroid	93[a]	7

Abbreviations: CNS, central nervous system; FH, fumarate hydratase.
[a]These statements represent those that reached a consensus.

DISCUSSION

Genetic risk assessment is the evaluation of an individual or family's risk of an inherited disease. This requires a detailed personal history, pedigree assessment, and comprehensive physical examination. Further testing in the form of single-gene or multigene sequencing is becoming increasingly available at numerous centers for appropriate candidates.[11] Although clinicians are at the front line and may be well positioned to recognize patients who need genetic risk assessment, barriers to initiating genetic testing include a lack of confidence to correctly identify optimal thresholds for initiating assessment, ability to discuss the risks and benefits, legal ramifications, and interpretation and explanation of genetic test results.[12] Indeed, adverse medical, legal, and financial incurrences have been documented as a result of cancer genetic testing without expert guidance.[13,14] An additional significant barrier is that of inconsistent reimbursement by insurance companies, likely caused in part by a lack of consensus guidelines for genetic testing, leading to limited accessibility for patients. Because referral guidelines for genetic evaluation remain vague, consensus recommendations may provide initial guidance in appropriate clinical scenarios.

The findings from this meeting represent the first consensus statement for genetic risk assessment in suspected hereditary RCC, addressing a critical gap in limited published guidelines. The European Association of Urology does not specify clinical criteria to initiate

risk assessment or genetic testing.[15] The updated 2021 NCCN guidelines, similar to the American Urological Association guidelines, now recommend genetic risk assessment for individuals with kidney cancer who are aged <46 years, have bilateral or multifocal renal masses, or have at least ≥1 first-degree or second-degree relative with RCC. In addition, the NCCN guidelines specify 5 tumor histologic subtypes that should prompt genetic risk assessment (hereditary leiomyomatosis and RCC-associated, Birt-Hogg-Dubé–associated, angiomyolipoma with 1 additional manifestation of tuberous sclerosis complex, SDH-deficient, and multifocal papillary RCC).[16,17] The American College of Medical Genetics and Genomics provides similar recommendations, with the addition of collecting duct and tubulopapillary RCC.[18] However, following these criteria alone will miss a significant proportion of hereditary RCCs and is insufficient to capture all clinical scenarios because of incomplete penetrance and diverse presentations of heritable disease.[5,9] Having suitable criteria will ensure that appropriate patients are evaluated, that they receive appropriate management, and that cascade testing is appropriately triggered. Being too broad, however, risks overwhelming a system in which access to genetic risk assessment is limited.

From this consensus panel meeting, in total, 30 statements met uniform consensus. The highest frequency of consensus was found in statements addressing who should be considered for genetic risk assessment. Most current guidelines discuss evaluation of individuals with a *strong* family history but do not clearly define which familial relationships are sufficient for evaluation.[15,18] Therefore, the recommendations from this panel to pursue further evaluation for individuals with RCC who have a first-degree relative or 2 second-degree (same lineage) relatives with RCC provide much needed clarity. In addition, the panel recommended that specific histologic diagnoses that may suggest germline aberrations (such as SDH-deficient, FH-deficient, and hybrid oncocytic tumors) should be sufficient indications for genetic evaluation, as well as multifocal or bilateral disease, which has been associated with an increased frequency of germline mutations.[5] Controversy in this subsection centered around age as a sole indication for genetic evaluation. Although early age of disease onset has been identified as a risk factor for identifying pathogenic germline mutations,[9] and syndromic cases have a propensity to present at a younger age,[3] concern was raised that an age alone *cutoff* would likely result in a high number needed to screen to identify positive cases.

In discussing when to initiate genetic risk assessment, the panel agreed that individuals who have a small renal mass (<3 cm) with suspicion for hereditary RCC should undergo genetic risk assessment before further oncologic management, as the diagnosis of a germline mutation could lead to delay or avoidance of surgery because of an increased propensity for the development of additional lesions in conditions such as VHL disease. There was also agreement that patients with multifocal or bilateral disease should undergo evaluation before management and that a histologic diagnosis may not be necessary. because several known hereditary syndromes are associated with bilateral and/or multifocal disease at presentation, including VHL disease, Birt-Hogg-Dube, hereditary papillary renal carcinoma, and hereditary leiomyomatosis and RCC, timely identification of a hereditary syndrome can significantly influence operative and nonoperative management.[19]

Determining what type of genetic test to use is an especially relevant question given the increasing number of commercially available testing options. Multigene panels have become more common, facilitating concurrent assessment of multiple cancer-associated genes and allowing a more comprehensive evaluation in the setting of a phenotype that is not highly suggestive of a single, specific mutation.[9] In our consensus panel, there was agreement that multigene panel testing was the approach of choice for suspected hereditary RCC in the absence of classic syndromic features. However, disadvantages of multigene panels include a higher rate of VUS detection as well as the identification of mutations associated with unrelated conditions, without clear evidence of how to interpret them in this context.[20,21] As such, there was nearly uniform consensus (83%) that, when a specific syndrome is suspected, only a single gene test should be pursued. Similarly, if an individual with a tumor mutation in a known RCC-associated gene were to pursue genetic testing, only single-gene germline testing should be performed.

Tumor profiling is being increasingly used in the setting of advanced cancer to identify actionable alterations that may be useful in the selection of systemic therapy. Unfortunately, in RCC, it is unclear how this information would guide therapy. Most of these tumor-based next-generation sequencing assays do not include parallel blood samples but test several genes known to be associated with hereditary cancer syndromes. In the setting of somatic tumor profiling, there was agreement that the decision to pursue genetic risk assessment should not be influenced by a negative somatic panel. In addition, germline mutations (especially incidental pathogenic variants)

may be missed on somatic testing because of issues of tumor purity and dilution of mutational frequency.[5] Nevertheless, some companies use their proprietary algorithms to predict germline mutations based on the depth of mutations identified by somatic testing.

How genetic risk assessment is performed must be determined in consideration of several factors. The American Society of Clinical Oncology recommends that all patients receive pretest counseling and provide written informed consent before genetic testing. Counseling should include discussion of outlined essential elements and should be performed by providers with experience in cancer risk assessment, especially for multigene panel testing.[22] Counseling by clinicians who lack genetics training may be impeded by often limited knowledge of the downstream impact of genetic testing, including health insurance coverage, implications for life insurance, and protections afforded by the Genetic Information Nondiscrimination Act. In addition, counseling may not always be reimbursed by some insurers, such as Medicare and Medicaid.[23] Referrals may be made to genetic counselors; however, with the rapid increase in genetic testing in recent years, a shortage of genetic counselors as well as limitations in access have been noted.[24] Telegenetics, or genetics consultations provided through telephone or video conferencing, may provide a viable option to meet this demand in areas with low availability of counselors.[25] Similarly, the use of web-based platforms and informational videos for pretest counseling and the direct disclosure of genetic test results to patients have been investigated for other types of cancers.[26,27] The findings of our consensus panel were in line with the American Society of Clinical Oncology recommendations, confirming that experienced clinicians may provide pretest counseling and suggesting that telehealth may be a sufficient option where there is a shortage of experienced providers. However, an informational video was not believed to be sufficient in pretest counseling for hereditary RCC, likely because of the heterogeneity in syndromes and the lack of established guidelines on what type of testing should be performed.

In the case of isolated extrarenal manifestations, the lack of consensus was influenced by the insufficient epidemiological data to determine accurate pretest probabilities of finding genetic mutations among those with a single clinical characteristic. For example, although the prevalence of skin leiomyomas may be estimated, because of the variable penetrance of genetic mutations associated with skin leiomyomas and RCC (such as in *FH*), the likelihood of identifying an *FH* mutation among all patients with a single skin leiomyoma is not known. Therefore, genetic risk assessment in the case of isolated extrarenal manifestations must balance the risk of over-testing with that of a missed diagnosis.

Although not all questions resulted in complete agreement and consensus, there a few strengths of the study that must be pointed out. For the current study, we used the Delphi methodology to generate and refine potential consensus statements as well as recruitment of an interdisciplinary, nationally renowned group of providers with expertise in hereditary RCC. Other published consensus panels for clinical recommendations have used similar methodologies with equally diverse groups of participants and found consensus on a similar percentage of proposed statements.[28-31] For example, a recent consensus panel on prostate cancer genetic testing, following a similar methodology, had a similar composition of urologists, medical oncologists, and genetic counselors.[32,33] Although such consensus statements may have various effects on clinical practice, we believe that the findings of this first ever consensus panel on genetic testing in hereditary kidney cancer has the potential for significant clinical utility because of the currently undefined best practices in this area.

Limitations of these consensus panel findings are primarily attributable to a lack of available high-level evidence supporting clear indications and optimal methodologies for the implementation of genetic testing in suspected hereditary RCC. In addition, whereas other consensus panels have relied on findings from previous consensus meetings in the same field,[32] to our knowledge, this represents the first guideline consensus statement for genetic risk assessment in hereditary RCC; therefore, recommendations were broadly stated. Finally, it should be noted that all panelists were from North American institutions; therefore, the findings should be interpreted in the context of regional disease patterns and resources in other parts of the world. Future directions include a follow-up meeting of consensus panel participants to refine statements in areas of controversy, including age alone cutoffs to prompt genetic risk assessment, the selection of single-gene versus multigene panels, the timing of genetic testing during workup and treatment of RCC, and interpretations of VUS.

In conclusion, these consensus statements from an expert panel address a critical gap in published guidelines for genetic risk assessment in hereditary RCC. The findings of this panel reflect an expert opinion on who, what, when, and how genetic evaluation should be performed and may serve as an initial guideline for providers treating

patients with suspected hereditary RCC. The identification of areas requiring further research and discussion represents an equally important finding given the rapidly evolving field. Future meetings are being planned to update and refine consensus statements and review areas of ongoing controversy.

CONFLICT OF INTEREST DISCLOSURES

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