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

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Abstract

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. Prior to the summit, a modified Delphi methodology was employed to generate, review, and curate a set of consensus questions regarding RCC genetic risk assessment. Uniform consensus was defined as at least 85% agreement to particular questions.

Results: Thirty-three panelists, including urologists (13), medical oncologists (12), genetic counselors and clinical geneticists (6), and patient advocates (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 with experience with hereditary RCC.

Conclusions: In the first ever consensus panel on RCC genetic risk assessment, 30 consensus statements were reached. Areas which 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.

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, we convened a multidisciplinary panel of national experts 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.

Precis

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 current 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.

Keywords

Genetic testing; Renal Cell Carcinoma; genetic assessment; germline mutations; recommendations; consensus

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 2–8% 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 disease (VHL), are highly penetrant with associated clinical manifestations which are rarely seen sporadically. However, newer RCC syndromes may have lower penetrance and fewer associated clinical manifestations. The Cancer Genome Atlas (TCGA) analysis and recent institutional series of advanced kidney cancer patient identified germline mutations in known cancer associated genes in 6–16% of submitted RCC cases[4], including those not previously believed linked to RCC[5]. There are now 15 genes with characterized alterations which 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 polymorphisms (SNPs)[8].

To assess an individual's genetic risk, a detailed personal and family history are considered essential elements of an initial evaluation, which can be further augmented by a comprehensive physical exam 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.

with 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 two 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 variable policies on coverage for germline testing, making it difficult for some patients to have access to appropriate care. In order to develop a working set of clinical recommendations for genetic testing for patients with diagnosis of or 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.

Methods:

Expert panel:

Prior to the inaugural 2019 Kidney Cancer Research Summit (KCRS) jointly sponsored by KidneyCAN (Philadelphia, PA) 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 (KCRS) who had relevant publications and/or expertise in hereditary RCC were invited. Additionally, 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]. Prior to 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 (Supplementary Table 1).

Consensus meeting:

The meeting was held on September 12th, 2019 in Philadelphia, PA. Prior to administration of the questionnaire, there was a brief presentation session summarizing the known genetic conditions, 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 recorded anonymously using the audience response system. After at least 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 was present. The level of consensus was defined in accordance with National Comprehensive Cancer Network (NCCN) criteria, which defines “uniform consensus” as at least 85% agreement, and general “consensus” as at least 50% agreement[10]. As 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, a total of 53 questions were included for panel review. These questions were grouped into five 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 extra-renal 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 (13), medical oncologists (12), genetic counselors and clinical geneticists (6), and patient advocates (2) (Supplementary Table 2).

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 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/without RCC who personally exhibited syndromic manifestations and those with/without RCC with family members with syndromic manifestations. It was agreed that further genetic risk assessment be performed for an individual with a first-degree relative or second degree relative (if no first degree relative 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 with a first degree or two second degree (same lineage) relatives with RCC undergo targeted genetic risk assessment. There was no consensus on testing unaffected individuals with first degree relatives with RCC, however it was agreed upon that having one 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 non-clear cell RCC histologies suggestive of succinate dehydrogenase deficient (SDH), fumarate hydratase (FH) deficient, or a hybrid oncocytic renal tumors. There was uniform consensus that patients with bilateral or multifocal renal tumors be offered genetic risk assessment, though there was a discussion that many of these patients, especially older individuals >60 years of age, would likely not require further testing or test negative.

The discussion of a cutoff age for genetic risk assessment was highly contentious. Participants felt 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. While 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, while others expressed that “age alone” may reliably guide the need for testing. For those supporting further genetic risk assessment based on threshold age, most agreed upon an age cutoff of 46 years old or less (67%).

When should genetic risk assessment be initiated?

Seven questions on when genetic risk assessment should be initiated were reviewed (Table 3). Panelists reached uniform consensus on only 2 (28.4%) questions. The panel agreed (93%) that for individuals with a localized renal lesion <3cm and a strong suspicion for a hereditary RCC syndrome, genetic risk assessment should be performed prior to management. Additionally, for those with a renal tumor and a suspicious associated skin lesion, there was consensus that a skin biopsy would not be required prior to 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 prior to management, but only limited agreement (57%) about the role of histologic diagnosis prior to initiating genetic risk assessment. Similarly, for individuals with a solitary renal tumor with one or more hereditary risk factors, 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 felt 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 pre-test counseling (100%), and that physicians such as urologists and oncologists with expertise in hereditary kidney cancer syndromes may themselves offer counseling prior to genetic testing (92%). As 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%) felt that a standardized video covering essential elements of pre-test counseling may be sufficient prior to testing. However, there was significant concern that this may not be sufficient without an opportunity for discussion with a qualified provider and further refinement of individualized

risk. If a non-standardized 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. While 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 VUS should be noted but not acted upon and patients should be managed based on standard clinical criteria.

Testing in cases of isolated extra-renal manifestations

Eight questions addressed pursuing testing for an isolated extra-renal 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%), endolymphatic sac tumor (100%), uveal melanoma (88%), and FH-deficient uterine fibroid (93%) should undergo genetic risk assessment and consideration of genetic testing. Other isolated extra-renal manifestations which 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.

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 exam. Further testing in the form of single or multigene sequencing is becoming increasingly available at numerous centers for appropriate candidates[11]. While clinicians are at the front line and may be well-positioned to recognize patients needing 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/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 due in part to a lack of consensus guidelines for genetic testing, leading to limited accessibility for patients. As 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 younger than the age of 46, have bilateral or multifocal renal masses, or have at least one first or second degree relative with RCC. In addition, the NCCN guidelines specify five tumor histologic subtypes which

should prompt genetic risk assessment (HLRCC-associated, BHD-associated, AML with one additional manifestation of tuberous sclerosis complex, SDH-deficient, and multifocal papillary RCC)[16,17]. The American College of Medical Genetics and Genomics provide similar recommendations, with the addition of collecting duct and tubulopapillary RCC[18]. However, following these criteria alone will miss a significant proportion of hereditary RCC, and are insufficient to capture all clinical scenarios due to 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 where access to genetic risk assessment is limited.

From this consensus panel meeting, a total of 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 “strong” family history, but do not clearly define which familial relationships are sufficient for evaluation[15,18]. Thus, the recommendations from this panel to pursue further evaluation for individuals with RCC with a first degree or two second degree (same lineage) relatives with RCC provide much needed clarity. Additionally, the panel recommended that specific histologic diagnoses which may imply germline aberrations (such as SDH, 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. While 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 in order to identify positive cases.

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

Determining what type of genetic test to employ 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 which 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 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 utilized in the setting of advanced cancer in order to identify actionable alterations which may be useful in selection of systemic therapy. Unfortunately, in RCC it is unclear how this information would guide therapy. Most of these tumor-based next generation sequencing (NGS) 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. Additionally, germline mutations (especially incidental pathogenic variants) may be missed on somatic testing due to issues of tumor purity and dilution of mutational frequency[5]. Nevertheless, some companies use their proprietary algorithms to predict germline mutations based on depth of mutations identified via somatic testing.

How genetic risk assessment is performed must be determined in consideration of several factors. The American Society of Clinical Oncology (ASCO) recommends that all patients receive pre-test counseling and provide written informed consent prior to genetic testing. Counseling should include discussion of outlined essential elements and be performed by providers with experience in cancer risk assessment, especially for multigene panel testing[22]. Counseling by clinicians lacking 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 (GINA). Additionally, counseling may not always be reimbursed by some insurers, such as Medicare and Medicaide[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 pre-test counseling and direct to patient results disclosures have been investigated for other types of cancers[26,27]. The findings of our consensus panel were in line with ASCO recommendations, confirmed that experienced clinicians may provide pre-test counseling, and suggested that telehealth may be a sufficient option where a shortage of experienced providers exist. However, an informational video was not felt to be sufficient for pre-test counseling for hereditary RCC, likely due to the heterogeneity in syndromes and lack of established guidelines on what type of testing should be performed.

In the case of isolated extra-renal manifestations, the lack of consensus was influenced by the insufficient epidemiological data to determine accurate pre-test probabilities of finding genetic mutations among those with a single clinical characteristic. For example, while

the prevalence of skin leiomyomas may be estimated, due to the variable penetrance of genetic mutations associated with skin leiomyomas and RCC (such as in fumarate hydratase (*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 extra-renal manifestations must balance the risk of over-testing with that of a missed diagnosis.

While not all questions resulted in complete agreement and consensus, there a few strengths of the study that must be pointed out. The present study 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 utilized 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]. While such consensus statements may have varying impact 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 due to 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 implementation of genetic testing in suspected hereditary RCC. Additionally, while 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, and therefore recommendations were broadly stated. Finally, it should be noted that all panelists were from North American institutions, and the findings should therefore 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 cut-offs to prompt genetic risk assessment, selection of single gene versus multigene panels, timing of genetic testing during workup and treatment of RCC, and interpretations of variants of unknown significance.

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. Identification of areas requiring further research and discussion represent 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Pooled participant specialties and practice information.

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 germline 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%)

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%**	0%
Should an individual without renal tumors and syndromic manifestations associated with hereditary kidney cancer be offered genetic risk assessment?	**100%**	0%
Should an individual with renal tumors and a first degree family member with syndromic manifestations (ex. pheochromocytoma, melanoma, pneumothorax) associated with hereditary kidney cancer be offered genetic risk assessment?	**96%**	4%
Should an individual without renal tumors and a first degree family member with worrisome syndromic manifestations (ex. pheochromocytoma, melanoma, pneumothorax) associated with hereditary kidney cancer be offered genetic risk assessment?	**95%**	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%**	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 relative should genetic risk assessment be offered?	**90%**	10%
For an individual with a renal tumor(s) and a first degree relative with RCC should genetic risk assessment be offered?	**90%**	10%
For an individual with a renal tumor(s) and two second degree relatives (same lineage) with RCC should genetic risk assessment be offered?	**87%**	13%
For an individual with a renal tumor(s) and one 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 one second degree relative with RCC should genetic risk assessment be offered?	11%	**89%**
In the absence of syndromic manifestations, should individuals with bilateral or multifocal renal tumors be offered genetic risk assessment?	**93%**	7%
Are there specific renal tumor histologies that should lead to recommendations for genetic risk assessment?	**97%**	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%**	0%
For individuals with histology suggestive of an FH deficient renal tumor, should genetic risk assessment be offered?	**100%**	0%
For individuals with histology suggestive of a hybrid renal tumor (Oncocytoma and chromophobe), should genetic risk assessment be offered?	**86%**	14%
Should those with bilateral or multifocal chromophobe RCC be recommended for genetic risk assessment?	**93%**	7%
Should those with bilateral or multifocal papillary type 1 RCC be recommended for genetic risk assessment?	**85%**	15%

Consensus question	Yes	No
Should those with bilateral or multifocal clear cell RCC be recommended for genetic risk assessment?	**93%**	7%
Should those with bilateral or multifocal renal angiomyolipomas be recommended for genetic risk assessment?	**86%**	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?		
a) 54 years of age (25th percentile) 17%	17%	
b) 46 years of age (10th percentile) 67%	67%	
c) 40 years of age (5th percentile) 7%	7%	
d) 36 years of age (2.5th percentile)	10%	

* Statements in bold represent those with reached consensus

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 prior to genetic risk assessment?	57%	43%
In the absence of syndromic manifestations, should an individual with a solitary renal tumor with one or more hereditary risk factors have a histologic diagnosis prior to 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 prior to management?	79%	21%
In the absence of syndromic manifestations, should an individual with a localized, solitary renal tumor with one or more hereditary risk factors have genetic risk assessment prior to management?	59%	41%
In an individual with a localized renal lesion less than 3 cm and strong suspicion for a hereditary cancer syndrome, should genetic risk assessment be performed prior to management?	**93%**	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%**

*Statements in bold represent those with reached consensus

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 at least one risk factor for hereditary kidney cancer be considered for single gene or multigene panel testing?	10%	**90%**
	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% **
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%**	3%
Should a negative somatic tumor profiling report (without germline testing) influence the decision to pursue genetic risk assessment?	39%	61%

* Statements in bold represent those with reached consensus

** 79% voted that the response to this question depends on the specific gene in question.

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*pre-test* counseling in patients suspected of having hereditary kidney cancer?	**92%**	8%
Is a standardized video covering essential elements of counseling sufficient for *pre-test* 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%**
If an individualized*pre-test* counseling was not performed, but germline testing is pursed, testing should:		
a) include a comprehensive cancer gene panel to avoid testing too narrowly	8%	
b) include a kidney specific gene panel only to keep focused	**92%**	
Is a telehealth/telegenetics visit with a licensed counselor sufficient for evaluation of individuals suspected of having hereditary kidney cancer?	**93%**	7%
Should individuals with variants of unknown significance (VUS) in genes that could explain a hereditary kidney cancer phenotype be treated as affected until more information if obtained?	56%	44%

*Statements in bold represent those with reached consensus

Table 6:

Which isolated extra-renal findings should prompt consideration of genetic risk assessment?*

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

*Statements in bold represent those with reached consensus