

## Canadian guideline on genetic screening for hereditary renal cell cancers

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### Abstract

**Background:** Hereditary renal cell cancer (RCC) is an ideal model for germline genetic testing. We propose a guideline of hereditary RCC specific criteria to suggest referral for genetic assessment.  
**Methods:** A review of the literature and stakeholder resources for

existing guidelines or consensus statements was performed. Referral criteria were developed by expert consensus.

**Results:** The criteria included characteristics for patients with RCC (age  $\leq 45$  years, bilateral or multifocal tumours, associated medical conditions and non-clear cell histologies with unusual features) and for patients with or without RCC, but a family history of specific clinical or genetic diagnoses.

**Conclusions:** This guideline represents a practical RCC-specific reference to allow healthcare providers to identify patients who may have a hereditary RCC syndrome, without extensive knowledge of each syndrome. RCC survivors and their families can also use the document to guide their discussions with healthcare providers about their need for referral. The criteria refer to the most common hereditary renal tumour syndromes and do not represent a comprehensive or exclusive list. Prospective validation of the criteria is warranted.

### Introduction

Renal cell carcinoma (RCC) is the eighth most commonly diagnosed cancer in Canada.<sup>1</sup> In 2012 there were an estimated 5600 new cases and 1700 deaths from RCC. In practice, RCC is a heterogeneous group of histologically distinct epithelial cancers originating in the renal parenchyma, including clear cell carcinoma (70%), papillary (15%), chromophobe (5%), collecting duct cancers, angiomyolipoma and oncocytoma.<sup>2</sup> At present, most RCCs appear to be sporadic and 5% to 8% hereditary. There are a number of well-defined hereditary RCC syndromes, each with their own specific clinical and molecular phenotypes (Table 1).

The American Society of Clinical Oncology recognizes the established role of germline testing of individuals at risk for hereditary cancers, including, but not limited to, cancers of the breast, ovary and colon.<sup>3</sup> Germline genetic testing is performed on non-tumour specimens (e.g., blood

**Table 1. Hereditary renal cell syndromes**

Genetic syndrome	VHL disease	Hereditary papillary RCC	Hereditary leiomyomatosis and RCC	BHDS	Tuberous sclerosis complex	Hereditary paraganglioma/pheochromocytoma
Histology	Clear cell RCC	Papillary type 1 RCC	Papillary type 2 RCC	Chromophobe RCC/oncocytic RCC	Epithelial (various) or mesenchymal (angiomyo-lipoma)	Clear cell RCC
Gene	<i>VHL</i>	<i>MET</i>	<i>FH</i>	<i>FLCN</i>	<i>TSC1</i> <i>TSC2</i>	<i>SDHB</i> <i>SDHC</i> <i>SDHD</i>
Germline testing	Yes	Yes	Yes	Yes	Yes	Yes
Target organs	Renal tumours CNS hemangioblastomas Retinal hemangiomas Adrenal pheochromocytoma/paraganglioma Pancreatic neuroendocrine tumours Endolymphatic sac tumours Epididymal cystadenomas Broad-ligament tumours	Renal only	Skin leiomyomas Renal tumours Uterine leiomyomas	Skin fibrofolliculomas Pulmonary cysts Renal tumours	Skin (adenoma sebaceum, shagreen spots) Retinal hamartomas CNS lesions (including tubers) Cardiac lesions Renal tumours Teeth/gum lesions Bone cysts	Adrenal pheochromocytoma/paraganglioma

VHL: Von Hippel Lindau disease; BHD: Birt-Hogg-Dubé syndrome; RCC: renal cell carcinoma; CNS: central nervous system.

or saliva) to determine inherited predisposition to specific cancers. Ideal tumour sites for germline genetic profiling have high penetrance mutations that translate into clinical utility, meaning they inform clinical decision-making and facilitate the prevention or amelioration of adverse health outcomes.

Hereditary RCC is an ideal model for germline genetic testing, since many of these syndromes have high RCC penetrance, established roles for cancer surveillance programs, specialized treatment algorithms (e.g., organ preservation) and opportunities for rational drug development.

There are many recent reviews of the clinical and genetic characteristics of hereditary RCC syndromes.<sup>2,4-8</sup> However, recommendations for referral for genetic assessment are typically generic (e.g., early age at presentation, bilateral tumours and family history) or sometimes not included. They often lack the details specific to the hereditary RCC syndromes and thus require the user to know or review each syndrome individually. We believe there is a need for a guideline with simplified hereditary RCC-specific referral criteria for genetic assessment.

The objective of our proposed guideline is to promote a reassessment of current practices of germline genetic screening for hereditary RCC. The scope is to define the characteristics of patients in the general population (all ages) who are at risk for hereditary RCC and who should be referred

for genetic assessment and counselling. The target audience for this guideline includes healthcare providers (primary care physicians, specialists [surgical and medical], genetic counsellors, laboratory geneticists and medical geneticists), payers, as well as patients (RCC survivors and others) and their families.

## Hereditary RCC

We describe the most common hereditary RCC syndromes and their associated conditions.

### von Hippel-Lindau syndrome

The most common and well-known of the hereditary RCC syndromes is the von Hippel-Lindau (VHL) syndrome (incidence 1:30 000-40 000).<sup>9</sup> This autosomal dominant condition results from the loss of function of the *VHL* tumour suppressor gene stimulating proliferation and angiogenesis. Identified mutations include point mutations, partial and complete deletions. The VHL syndrome includes combinations of central nervous system (CNS) or retinal hemangioblastomas, pheochromocytomas, RCC, endolymphatic sac tumour, papillary cystadenoma of the epididymis, broad ligament tumours and neuroendocrine tumours of the pancreas. Malignant RCC (clear cell type) occurs in 35% to 75% of affected individu-

als (mean age at diagnosis of 40 years). This syndrome has well-defined and effective cancer screening recommendations for diagnosed VHL patients, starting as early as 2 years of age.<sup>10</sup> In contrast to sporadic clear cell RCC, but similar to other hereditary RCC syndromes, there are clear genotype-phenotype relationships, with different patterns of risk in different family pedigrees. Specific genotypes, therefore, mandate family-specific screening and surveillance.<sup>11</sup>

### Hereditary papillary RCC

Hereditary papillary RCC (HPRCC) is an autosomal dominant condition associated with a germline mutation of the *MET* proto-oncogene.<sup>9</sup> *MET* is a receptor tyrosine kinase which, when mutated, leads to autophosphorylation of the receptor and increased downstream signaling. Patients present with type 1 papillary RCC are characterized by either multiple/bilateral tumours and/or a family history of RCC. Metastatic potential is low. Surveillance of small tumours and nephron-sparing surgery for larger tumours are key tenets of management.

### Hereditary leiomyomatosis and RCC

Hereditary leiomyomatosis and RCC (HLRCC) is caused by autosomal dominant mutations in the fumarate hydratase gene which encodes an enzyme involved in the tricarboxylic acid (Krebs) cycle.<sup>9</sup> These mutations lead to derangements in cellular aerobic and anaerobic metabolism. Clinical dermatologic diagnosis requires multiple cutaneous leiomyomas or a single lesion with a positive family history. Uterine leiomyomas are usually multiple and large (mean age at diagnosis 20-35 years). Estimates of the penetrance of papillary type 2 RCC vary tremendously and have been as high as 50%, though more often quoted at 10% to 20%. Papillary type 2 RCC is much more aggressive than type 1 and is prone to early metastases and local invasion, mandating much more aggressive surgical management.

### Birt-Hogg-Dubé syndrome

Birt-Hogg-Dubé syndrome (BHDS) is a rare autosomal dominant condition associated with mutation of the folliculin gene (*FLCN*) gene, which produces a protein by the same name that is involved in the AMPK and mTOR pathways.<sup>9</sup> BHDS is manifest by a triad of dermatological findings: fibrofolliculomas, trichodiscomas and acrochordons (skin tags). Only fibrofolliculomas are specific for BHDS. These typically appear in the third to fourth decade of life. Pulmonary cysts and pneumothorax can develop in 20% of patients. Affected individuals are known to develop various types of RCC, including oncocytic, chromophobe and, less commonly, clear cell and papillary histologies. Metastatic potential is usually low. Surveillance of small tumours and

nephron-sparing surgery for larger tumours are typically key components of the management.

### Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is an autosomal dominant condition, caused by mutations and loss of function for the *TSC1* gene and *TSC2* gene, each of which encode growth inhibiting proteins known as hamartin and tuberin respectively.<sup>9</sup> Loss of *TSC1* or *TSC2* gene function results in increased mTOR activity. TSC occurs in 1:5800 live births. Diagnostic criteria include cutaneous findings (fibromas, plaques and nevi), retinal and CNS lesions, cardiac tumours and renal tumours. Renal tumours only appear in 2% to 4% of patients and can be either epithelial (cysts or tumour of various types) or mesenchymal (angiomyolipomas).

### Hereditary paraganglioma/pheochromocytoma

Hereditary paraganglioma/pheochromocytoma is an autosomal dominant condition caused by mutations in subunits of the succinate dehydrogenase complex (*SDHB*, *SDHC*, *SDHD* genes), which encodes an enzyme involved in the tricarboxylic acid (Krebs) cycle.<sup>9</sup> Benign and malignant tumours arise from the adrenal medulla (pheochromocytoma) or extra-adrenal (paraganglioma) autonomic nervous tissue. Patients with this condition are at an increased risk of RCC.

While not constituting a syndrome, a series of constitutionally balanced chromosome 3 translocations affect gene expression and are associated with the development of RCC.<sup>12</sup> Diagnosis of the predisposition is via karyotyping. The genes associated with this predisposition have not been identified.

### Methods

A review of the literature was conducted to look for guidelines or consensus statements regarding genetic assessments for RCC or the most common hereditary RCC syndromes using the MEDLINE database (from 1946 to present). Search queries included MESH terms renal cell carcinoma, renal neoplasms, hereditary cancer, von Hippel-Lindau Disease, Leiomyomatosis, Tuberous Sclerosis, guideline, genetic screening, Genetic Testing, Genetic Counseling and Genetic Predisposition to Disease. Natural language and text word combinations included hereditary renal, familial renal, hereditary RCC, familial RCC, hereditary papillary, Birt-Hogg-Dubé syndrome, genetic testing, genetic screening and genetic counselling. Results were restricted to the English language.

In addition, we reviewed online resources of the National Guideline Clearinghouse, National Comprehensive Care Network guidelines, Canadian College of Medical Geneticists, American Colleges of Medical Geneticists

and Genomics, National Society of Genetic Counselors, Canadian Association of Genetic Counselors and the Canadian, American and European Urologic Associations.

## Results

The literature review did not reveal any validated referral criteria for genetic assessment for hereditary RCC syndromes. The only guideline identified was by the Alberta Health Services for the identification of patients at risk of *VHL* gene mutation, which was based on a review of literature and expert opinion.<sup>13</sup>

Therefore, our recommendations represent a broader guideline for the most common hereditary RCC syndromes and are similarly based on literature review and expert consensus (Table 2).

Early age at presentation, bilateral or multifocal tumours and family history represent generic criteria that suggest a possible hereditary cancer syndrome irrespective of the organ involved.<sup>6</sup> Specifically for RCC, our age cutoff was based on recent American data suggesting the median age for hereditary RCC at 37 years; 70% of hereditary RCC tumours would be found in the lowest decile ( $\leq 45$  years old) of all RCC tumours.<sup>14</sup> Having a positive family history for RCC has been shown to be a risk factor for RCC with a relative risk of 2.2.<sup>15</sup> The remainder of the criteria reflects documented characteristics of specific hereditary cancer syndromes.

## Discussion

This guideline represents a practical RCC-specific reference to allow healthcare providers to identify patients who may have a hereditary RCC syndrome, without extensive knowledge of each syndrome. As well, RCC survivors can use the document to guide their discussions with healthcare providers about their need for referral.

The criteria refer to the most common hereditary renal tumour syndromes and do not represent a comprehensive or exclusive list. They also do not include criteria for referring individuals with renal tumours that may be present in families with other well-established hereditary cancer predisposition syndromes, such as Lynch Syndrome (i.e., upper tract urothelial tumours). Well-established criteria for referral to genetic assessment for such families currently exist.<sup>16</sup>

As with pheochromocytoma, there is the possibility of an underestimation of the prevalence of hereditary RCC, in particular in non-syndromic cases due to low penetrant mutations.<sup>17</sup> Uncommon and new emerging entities of RCC may also represent sources of hereditary cases.<sup>18</sup>

The benefit of identifying hereditary RCC is to inform the medical management of affected individuals. As well, the identification of a single affected family member frequently leads to the diagnosis of a hereditary predisposition in other asymptomatic family members; surveillance can then be offered to these family members before any cancer

**Table 2: Criteria for referring patients with renal tumours for genetic assessment**

1. Patients with any renal tumour (benign or malignant) AND any one of the following:
  - a. **Bilaterality** or **multifocality**
  - b. **Early age of onset** ( $\leq 45$  years of age)
  - c. **1st or 2nd degree relative** with any renal tumour
  - d. A history of **pneumothorax\***
  - e. One of the following **dermatologic findings**:
    - i. Skin leiomyomas\*
    - ii. Skin fibrofolliculomas/trichodisomas\*
  - f. One of the following **associated tumours**:
    - i. Pheochromocytoma/paraganglioma\*
    - ii. Hemangioblastoma of the retina, brainstem, cerebellum or spinal cord\*
    - iii. Early onset of multiple uterine fibroids ( $< 30$  years of age)\*
  - g. Lymphangiomyomatosis\*
  - h. Childhood seizure disorder\*  
(\*or 1st degree relative with same)
2. Patients with **non-clear cell** carcinoma with unusual associated features (e.g., chromophobe, oncocytic or hybrid tumours)
3. Patients, with or without RCC, who report a family member (any) with a known **clinical or genetic diagnosis** of any one of the following:
  - a. Von Hippel-Lindau syndrome
  - b. Birt-Hogg-Dubé syndrome
  - c. Hereditary leiomyomatosis and renal cell cancer
  - d. Hereditary papillary renal cell cancer
  - e. Hereditary paraganglioma/pheochromocytoma
  - f. Tuberous sclerosis

develops.<sup>19,20</sup> In addition to identifying patients with newly diagnosed RCC who have cancer predisposition syndromes, it is hoped that this guideline will raise awareness of the risk of RCC in patients with associated non-urologic conditions (e.g., dermatologic or respiratory).<sup>8,21</sup>

Unfortunately, there are potential harms associated with the identification of hereditary RCC syndromes.<sup>3</sup> Potential harms include psychological stress related to knowledge of increased risks to themselves or their family members, concerns about employment or insurance discrimination, stigmatization and confidentiality.

Genetic assessment might take the form of referral to a genetics clinic with qualified medical geneticists and genetic counsellors, or to an alternate equivalent model with properly trained individuals who can address the pros and cons of genetic testing and assist the patient in making an informed decision.<sup>22</sup> We believe that genetic counsellors should be routinely integrated within cancer care programs and that genetic considerations become a standard part of the multidisciplinary discussion for every patient.

The scope of this document was to define criteria to identify patients at risk of hereditary RCC. No recommendation is made regarding specific genetic testing methods or platforms. Germline testing is available at a limited number of genetic laboratories within Canada and more widely in the

United States.<sup>23</sup> We note that mutation detection is challenging in both sporadic and hereditary RCC syndromes, where loss-of-function mutations are dispersed throughout the tumour suppressor genes involved, in contrast to conserved hot-spot oncogenic mutations in other cancers (e.g., BRAF<sup>V600E</sup> in melanoma). Whole genome next-generation digital sequencing platforms are just beginning to affect clinical practice. When massively-multiplexed with pooled barcodes, next-generation sequencing platforms may allow targeted deep sequencing, which should allow more comprehensive assessment of genotypic changes and have cost advantages over traditional Sanger sequencing.<sup>24</sup>

A limitation of this guideline is that it has not addressed the cost-benefit ratio of genetic screening for each syndrome. The incremental cost of genetic counselling, and the more substantial cost of cancer surveillance for affected patients and their families, could offset the costs associated with the late diagnosis of hereditary cancers both from a healthcare perspective and in terms of morbidity and mortality.

## Conclusion

Validation of these criteria is required. A potential validation cohort is the new Canadian Kidney Cancer Information System (CKCis) that is collecting data on all RCC patients diagnosed in 13 participating centres.

The Kidney Cancer Research Network of Canada Genetics Initiative will review the guideline at least every 2 years.

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for Amgen and Actavis (formerly Watson). He has also been an investigator in clinical trials run by Cancer Care Manitoba (CCMB). Dr. Kapoor is a member of the Speakers bureau for Pfizer Oncology and Novartis Oncology. Dr. Kassouf is an Advisory Board member and a speaker for Amgen and Astellas. He has also received grants and honoraria from these companies. He is currently participating in unpaid clinical trials within the past 2 years.

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