There are many inherited renal cell cancer syndromes that increase an individual's risk of developing renal cell cancer. The age of onset for these renal cell cancer syndromes ranges from infancy to age 65 years. Clinical manifestations vary widely, and multiple body systems can be involved and present unique challenges to the healthcare team. With the advancement of genetic panels, clinicians can screen individuals with known hereditary syndromes for genetic mutations. This article offers clinically relevant information specific to various major renal cell cancer syndromes.

AT A GLANCE

- Most renal cell cancer syndromes are autosomal dominant and increase an individual's risk of developing renal cell cancer and other malignancies.
- A wide range of clinical manifestations include benign and malignant histology.
- Heightened surveillance and preemptive management of individuals with known renal cell cancer syndromes can improve outcomes and quality of life.

KEYWORDS
hereditary renal cell cancer syndromes; mutation; autosomal dominant; genetics

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Renal Cell Cancer Syndromes

Identification and management of patients and families at increased risk

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Individuals with inherited renal cell cancer syndromes develop kidney cancer at an earlier age with notable features of heterogeneous, multifocal, and bilateral tumors. Several of the syndromes have renal cell cancer as a primary feature, including von Hippel-Lindau syndrome and Birt-Hogg-Dubé syndrome, whereas others, such as Lynch syndrome and Cowden syndrome, have renal cell cancer as a secondary feature. Most hereditary renal cell cancer syndromes are autosomal dominant, meaning that only one copy of the mutated gene is needed to be present to express the disease. The mutated gene predisposes affected individuals to tumor development, often with early-onset malignancy (da Costa et al., 2017). Children of parents with autosomal dominant diseases have a 50% chance of inheriting the syndrome. Each hereditary renal cell cancer syndrome manifests with different clinical symptoms and is correlated with varying risks of developing renal cell cancer. This article presents clinically relevant information on hereditary renal cell cancer syndromes associated with renal cell cancer, with a focus on the incidence, background, and clinical implications (see Table 1).

Hereditary Renal Cell Cancer Syndromes

von Hippel-Lindau Syndrome

von Hippel-Lindau syndrome is the most common hereditary renal cell cancer syndrome. It is characterized by visceral cysts and benign tumors that have the potential to become malignant. Individuals with von Hippel-Lindau syndrome have a 40% chance of developing renal cell cancer (Gupta et al., 2017). However, the loss of *VHL* gene function alone is not enough for patients to develop renal cell cancer. Other gene mutations in conjunction with *VHL*, including *BAP1*, *PBRM1*, *JARID1C*, *SETD2*, and *KDM6A*, have been found in patients with renal cell cancer, indicating that multiple gene mutations are involved with renal cell cancer development (Gossage et al., 2014). *SDHB* and *TMEM127* alterations have been linked to *VHL* mutations, but their connection to renal cell cancer is unclear (Gupta et al., 2017). Additional research is necessary to determine the exact relationship among *SDHB*, *TMEM127*, *VHL*, and renal cell cancer.

Lynch Syndrome/Hereditary Nonpolyposis Colorectal Cancer

Lynch syndrome, synonymous with hereditary nonpolyposis colorectal cancer, is a condition that predisposes individuals to an increased risk of colorectal cancer, endometrial cancer, upper tract urothelial cancers, and other types of cancers (Lynch et al., 2015). A number of germline mutations are associated with Lynch syndrome, specifically in the mismatch repair genes. These genes are responsible for correcting mismatched nucleotides when DNA is copied in preparation for cell division. Germline mutations in the *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes (members of the MMR