von Hippel-Lindau (VHL) Disease

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Dr. Eric Jonasch, MD
Professor of Medicine
UT MD Anderson Cancer Center
Vice Chair of NCCN Kidney Cancer Guidelines

Presentation Outline

- **VHL Disease Overview**
- **Epidemiology**
  - Incidence, prevalence and penetrance of VHL
  - RCC
- **Burden of illness**
  - VHL's impact on QoL
  - Emotional, physical, psychosocial challenges
- **VHL Treatment : Recent FDA Approval**
- **Current Standard of Care**
  - VHLA Guidelines
  - NCCN Guidelines
- **Implications and Rationale for new ICD-10-CM Code Request**
  - Improved clinical management
  - Improving understanding of disease and its manifestations
  - Improved care access

RCC: Renal Cell Carcinoma; VHL: von Hippel Lindau; NCCN: National Comprehensive Cancer Network; VHLA: VHL Alliance; QoL: Quality of Life

von Hippel-Lindau Disease Overview

Background /

- VHL disease is a rare genetic disorder caused by mutation, deletion or hypermethylation in the VHL gene, a tumor-suppressor gene located on chromosome 3p25-26.
- VHL disease can be inherited in an autosomal dominant manner; however, VHL mutations can also arise de novo
- Insufficient VHL ICD-10 coding leads to the difficulty of robust research and adequate patient treatment for the rare disease

Rationale For New Code /

- An ICD-10-CM code specific to VHL will differentiate VHL from other diseases and will ultimately lead to:
  - Improved clinical management
  - Improved recording of VHL disease in clinical practice
  - Greater epidemiologic and real-world healthcare services research on VHL
  - Improved tracking and specific identification of individuals with VHL disease
    - Potential for faster access to specific treatments

VHL: von Hippel-Lindau
Source: Renal Cell Carcinoma in von Hippel–Lindau Disease—From Tumor Genetics to Novel Therapeutic Strategies. Available here

Patients With VHL Are At Increased Risk of Developing Various Benign and Malignant Tumors and/or Cysts

The Manifestations of VHL Disease Include:

- Renal cysts
- Renal Cell Carcinoma (RCC)
- Pheochromocytomas
- Retinal hemangioblastomas
- Central nervous system (CNS) hemangioblastomas
- Liver hemangiomas
- Pancreatic cysts
- Pancreatic microcystic serous adenomas
- Pancreatic neuroendocrine tumors (pNET)
- Epididymal and broad ligament cystadenomas
- Endolymphatic sac tumors

Sources:
1.Tumors in von Hippel-Lindau Syndrome: From Head to Toe-Comprehensive State-of-the-Art Review. Available here
2. Management of von hippel-lindau disease: an interdisciplinary review. Available here
3. Active Surveillance for von Hippel-Lindau-Related Renal Tumors using Size-Based Risk Stratification: Longterm Results. Available here
VHL: von Hippel-Lindau

The Majority of Patients with VHL Disease Develop Clinical Symptoms Before the Age of 65

Incidence

- The incidence of VHL disease in the U.S. is thought to be about one in 36,000 births with an estimated de novo mutation rate of 4.4x10- 6 gametes per generation

Prevalence

- The prevalence of VHL disease in the U.S. ranges from 1 in every 30,000 people to 1 in every 50,000 people
- 10,000 people estimated to be living with the disease

Penetrance

- VHL disease has a high penetrance rate
  - Approximatively 90% by the age of 65 years, leading to early-onset of the disease

RCC

- RCC is the most frequent visceral manifestation and most frequent type of malignant tumor in VHL disease
- In the US, the reported frequency of RCC in VHL disease is estimated at 42-57.5%

Sources:
1.Active Surveillance for von Hippel-Lindau-Related Renal Tumors using Size-Based Risk Stratification: Longterm Results. Available here
2. NORD. Von Hippel-Lindau Disease. Available here
3. Von Hippel Lindau Syndrome. Available here
4. Age at diagnosis is a determinant factor of renal cell carcinoma–specific survival in patients treated with nephrectomy. Available here
5. VHL gene mutations in renal cell carcinoma: role as a biomarker of disease outcome and drug efficacy. Available here
VHL: von Hippel-Lindau; RCC: Renal Cell Carcinoma

Patients with VHL Experience Numerous Challenges That Negatively Impact Their Overall Quality of Life

Physical and Psychosocial Challenges /

- Little reprieve from caregiving responsibilities
- Difficulties balancing the needs of VHL-affected and other unaffected family members
- Fears about the future
- Guilt regarding the onset of tumors in their children
- Kidney function decline from tumor reduction surgery
- Declining work productivity due health related uncertainties

Emotional Distress Associated With /

- The wide number of possible manifestations
- Variable age of onset - from early childhood into adulthood
- The ‘watch and wait’ approach of active surveillance
- Burden of lifelong treatment

Sources:
1. Von Hippel-Lindau disease: molecular pathological basis, clinical criteria, genetic testing, clinical features of tumors and treatment. Available here
2. Psychosocial impact of Von Hippel-Lindau disease: levels and sources of distress. Available here
VHL: von Hippel-Lindau

The VHL Alliance is The Preeminent Resource and Clearinghouse For Those Affected by VHL Disease

The **VHLA Surveillance Guidelines** recommend testing of patients who are at risk of VHL disease who do not yet have symptoms, and patients who do not have VHL disease symptoms in a particular area, including screening of unaffected organs as follows:

- Patients presenting with signs/symptoms should be evaluated with appropriate testing/imaging regardless of age
- Surveillance testing should ideally be performed prior to any planned conception, if possible. MRIs performed during pregnancy should be without contrast
- Modifications of surveillance schedules with more frequent testing may be needed to track the growth of known lesions
- Beginning at age 65, routine laboratory and radiologic screening for patients who have never had specific VHL manifestations may cease, with the exception of routine physical examination and ophthalmologic assessment
- The VHL Alliance Guidelines make several recommendations for the MRI of the brain and spine, or abdomen, with or without contrast every 2 years (e.g., macrocyclic/class II gadolinium-based contrast agents should be used, the neuroaxis protocol and the abdominal protocols should be obtained consecutively, it is not recommended to evaluate the spine solely using an abdominal protocol MRI).

Sources:
1. Von Hippel-Lindau Syndrome. Available here
2. VHL Alliance. VHLA Suggested Active Surveillance Guidelines. Available here
VHL: von Hippel-Lindau; VHLA: von Hippel-Lindau Alliance; MRI: Magnetic Resonance Imaging

FDA Approves Merck's Hypoxia-Inducible Factor-2 Alpha (HIF-2α) Inhibitor, Belzutifan

Breakthrough Therapy Designated Drug, Belzutifan, Has Been Approved for Adult Patients With VHL Disease Who Require Therapy for Associated RCC, CNS Hemangioblastomas, or pNET, Not Requiring Immediate Surgery

A Specific ICD-10-CM Code For VHL Provides Several Benefits For Patient Who Need Access To New Therapies /

Tracking and Monitoring

- Better able to identify patients and track appropriate treatment
- Improved adherence to practice guidelines, better tracking of adverse events

Support Screening and Treatment

- Enable screening for secondary cancers found in VHL disease
- Enable faster access for novel therapeutics and treatments

Research

- An ICD-10-CM code specific to VHL-related disease will facilitate epidemiologic and health services research for this disease potentially leading to development of new diagnostic and treatment options in future

VHL: von Hippel- Lindau; RCC: Renal Cell Carcinoma; CNS: Central Nervous System Hemangioblastomas; pNET:
Source: Merck. News Release. Available here

NCCN Guidelines for Kidney Cancer Includes Guidance on Diagnosis, Screening and Surveillance for VHL

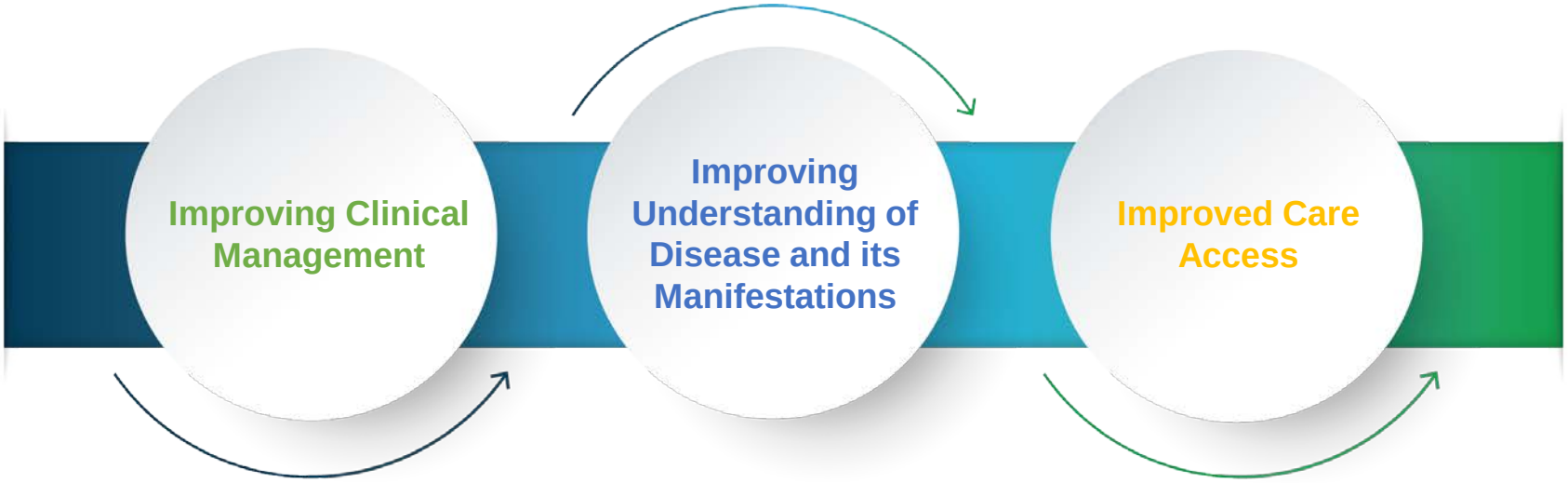
People with VHL may receive care from VHL Alliance Clinical Care Centers which consists of teams of VHL disease specialists

- Genetic testing is recommended in individuals with a close blood relative (first-degree or second-degree) with a known VHL pathogenic/likely pathogenic variant
- Genetic counseling is recommended in individuals with RCC who present disease features/ clinical manifestations of VHL disease
- The NCCN recommends referral to cancer genetics professionals for individuals with RCC

In addition to the recently FDA approved belzutifan, there are other products in development, however specific coding would improve patient identification, diagnosis and treatment

Sources:
1. VHL Alliance Clinical Care Centers. Available here
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Available here
VHL: von Hippel-Lindau; NCCN: National Comprehensive Cancer Network; FDA: Food and Drug Administration; RCC: Renal Cell Carcinoma

The Ability to Code Accurately Should Allow More Precise Healthcare Services Research and Ultimately Lead to Improved Patient Outcomes



- Improved coding sensitivity for VHL disease
- Better reporting and identification of VHL patients in routine clinical practice
- Timely and appropriate screening, testing and intervention

- Increased epidemiologic and health services research for VHL
- Greater access to EMR, administrative databases and other large RWE datasets

- Clearly identifying patients with VHL disease will enable greater access of novel therapeutics and treatments

Given the early onset and high burden of VHL disease, an improved understanding of the disease and its management is needed to help clinicians, researchers, and payers/policymakers alike provide best possible care for these patients

Source: Phakomatoses: A pictorial review. The Indian journal of radiology & imaging. Available here
VHL: von Hippel-Lindau; EMR: Electronic Medical Records; RWE: Real World Evidence

Appendix

FDA Approves Merck's Hypoxia-Inducible Factor-2 Alpha (HIF-2α) Inhibitor Belzutifan

Belzutifan Has Been Approved for Adult Patients With VHL Disease Who Require Therapy for Associated RCC, CNS Hemangioblastomas, or pNET, Not Requiring Immediate Surgery

Data Supporting Belzutifan's Approval /

Belzutifan's Approval Is Based On An Open-Label Clinical Trial Involving 61 patients With VHL-Associated Tumors			
	VHL-Associated RCC	**VHL-Associated CNS Hemangioblastomas**	**VHL-Associated pNET**
ORR %	49%	63%	83%
Complete Response Rate	-	4%	17%
Partial Response Rate	100%	58%	67%
DoR Range (months)	2.8+ to 22.3+	3.7+ to 22.3+	10.8+ to 19.4+
% of Patients Responding After 12 Months	56%	73%	50%
Median TTR- (months)	8	3	8
Median TTR Range (months)	2.7 to 19	3-11	3 to 11
Efficacy endpoints for the study included ORR, DoR, and TTR			

As more treatments become available, an ICD-10-CM code will aid in identifying patients and track appropriate treatment and further adherence to practice guidelines

VHL: von Hippel- Lindau; RCC: Renal Cell Carcinoma; CNS: Central Nervous System Hemangioblastomas; pNET: Pancreatic Neuroendocrine Tumors; ORR: Objective Response Rate; DoR: Duration of Response; TTR: Time to Response
Source: Merck. News Release. Available here