2018 ANNUAL MEETING
SUMMARY OF PRESENTATIONS

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Elaine Lam, MD FACP, Medical Oncologist, Associate Professor of Medicine, Co-Director of the Urologic Oncology Clinic, and member of the VHL Clinical Care Center at University of Colorado, Anschutz Medical Campus, introduced some background information on VHL. She also discussed the importance and value of regular surveillance for patients with VHL.

Von Hippel-Lindau Disease, or VHL, is an inherited, autosomal dominant condition that occurs in about 1 out of every 36,000 people. It results from a germline mutation in the VHL gene, which is a tumor suppressor gene. 20% of cases are considered de novo, or “first-in-family”, which means that they do not have a family history of VHL disease. The VHL gene is located on the short arm of chromosome 3 and everyone has two copies of it. VHL is an autosomal dominant condition, which means that those who have VHL have a 50% chance of passing on the mutation to each of their children.

VHL is a disease that involves a higher risk of developing non-cancerous and cancerous tumors. Some of the possible non-cancerous tumors include: renal, pancreatic, and epididymal cysts, central nervous system (CNS) hemangioblastomas, retinal hemangioblastomas, and endolymphatic sac tumors (ELSTs). Some of the possible cancerous tumors include: kidney cancer/renal cell carcinoma (RCC), pheochromocytoma (pheochromocytomas) and pancreatic neuroendocrine tumors (pNET).

There are two classifications of VHL: Type 1 and Type 2. Type 1 VHL is characterized by a low risk for pheochromocytomas, but a high risk for hemangioblastomas and RCC. There are three different Type 2 subtypes, all of which are characterized by a high risk for pheochromocytomas. Type 2A may involve a high risk for hemangioblastomas and pancreatic tumors, but low risk for RCC. Type 2B may involve a high risk for hemangioblastomas, pancreatic tumors and RCC. Type 2C may be high risk for pheochromocytomas only.

CNS hemangioblastomas occur in about 60-80% of people with VHL. They are most common in the cerebellum, spinal cord and brainstem. They can enlarge over time, but are typically benign and won’t spread to other parts of the body. The main treatment in usually surgical resection, although stereotactic radiosurgery may be an option in specific cases. CNS hemangioblastomas are an important cause of physical disability in people with VHL. Symptoms may include headaches and dizziness, as well as, pain, tingling and numbness in the arms, legs and back.

Retinal hemangioblastomas are similar to those in the CNS, except that they are located in the retina of the eyes. About 25-60% of people with VHL will develop retinal hemangioblastomas and they will develop in both eyes in about 50% of cases. The main complication from these tumors is visual loss, occurring in about 35% of cases. They are diagnosed via a dilated retinal exam by an ophthalmologist, with retinal angiography if needed. Depending on the specific details of each tumor, the main treatment for smaller tumors is laser photocoagulation, whereas the main treatment for larger and peripheral ones is cryotherapy. New anti-angiogenic therapies are currently being investigated.

The most frequent malignant tumor associated with VHL is clear cell renal cell carcinoma (RCC). The risk for developing RCC is highest for Type 1 and Type 2B VHL patients, with a lifetime risk of about 70%. There is also a high risk for multiple and bilateral RCC, occurring in about 30-60% of cases. The average age of RCC diagnosis is about 25 to 50 years. While many RCCs may be detected during routine screening, most grow slowly and usually do not require immediate intervention. Because VHL-related RCC tends to be bilateral, multiple, and recur over time, these can generally be observed until the largest tumor reaches 3cm. This is because there is virtually no metastatic potential for RCCs less than 3cm, whereas there is a 35% risk of metastasis for RCCs that are greater than or equal to 3cm. The optimal approach to treatment is one that preserves as much kidney function as possible, such as partial nephrectomy or radiofrequency ablation or cryotherapy.
Pheochromocytomas (pheochromocytomas) are common in all those who have Type 2 VHL. The average age of diagnosis is about 12 to 25 years. The overall risk of malignancy in VHL-related pheochromocytomas is about 2.5-5%, which is lower than the risk for people with non-VHL-related pheochromocytomas. Symptoms may arise as a result of too much adrenaline and may include headaches, sweating, anxiety, agitation, as well as cardiac complications, including heart attack, stroke, palpitations and heart failure. The treatment for pheochromocytomas is surgical resection.

Pancreatic tumors and cysts are very common in VHL. Pancreatic neuroendocrine tumors (pNETs) occur in about 12-17% of people with VHL. pNETs should be considered for surgery when they are larger than 3cm or have a tumor doubling time less than 500 days. (Research by Dr. Amit Tirosh has shown that an exon 3 VHL mutation is another indicator for surgery, as it is associated with an increased risk for metastasis.)

Endolymphatic sac tumors (ELSTs) occur in up to 11% of people with VHL, with an average age of diagnosis of 22 years, and there is a high risk for developing them in both ears. Bilateral ELST is pathognomonic for VHL disease. These tumors come from the endolymphatic sac, which is involved with inner ear fluid homeostasis. If left untreated, they can invade into bone in the skull and grow into nerves. Symptoms may include hearing loss, tinnitus, vertigo and ear fullness. The best treatment is early detection and surgical resection.

While a definite diagnosis of VHL is through genetic testing, a clinical diagnosis of VHL disease is often made based on one of the following combinations of findings: One index tumor (hemangioblastoma, pheochromocytoma, RCC) and a positive family history, two or more CNS hemangioblastomas, or one CNS hemangioblastoma with one visceral manifestation. Genetic testing can be performed via a blood test or a cheek swab. The following people should be referred for genetic testing:

- Any blood relative of a person with VHL
- Individuals with one VHL-associated lesion and a positive family history of VHL-associated lesions
- Individuals with two VHL-associated lesions should also be referred for genetic testing
- Individuals with any of the following:
  - RCC diagnosed earlier than 40 years old
  - Bilateral or multiple RCCs
  - RCC with positive family history
  - Hemangioblastoma diagnosed earlier than 30 years old
  - More than 2 CNS hemangioblastomas
  - Hemangioblastoma and a RCC, pheo or pNET
  - Pheo diagnosed earlier than 40 years old
  - Bilateral or multiple pheochromocytomas
  - Pheo and positive family history
  - More than 1 pancreatic serous cystadenomas
  - More than 1 pNET
  - Multiple pancreatic cysts and any VHL-associated lesion

Molecularly speaking, the VHL gene functions as a tumor suppressor gene and helps with the normal breakdown of proteins called hypoxia inducible factors (HIF). When functioning properly, HIF proteins are degraded. When there is a mutation in the VHL gene, HIF proteins do not get degraded and turn on other proteins that stimulate growth. Over the years, VHL research has resulted in a number of treatments for RCC, not just for people with VHL. There are currently a number of ongoing clinical trials for drugs being evaluated to treat VHL-related tumors, including pazopanib, axitinib, cabozantinib, and PT2977.
It is of paramount importance that all people with VHL, regardless of type, undergo ongoing surveillance throughout their lives, beginning in childhood. Current screening guidelines for CNS hemangioblastomas call for MRI scans of the head and spine every 12-36 months, beginning the first year of life in children with genetically diagnosed VHL syndrome, especially in adolescents. Screening for retinal hemangioblastomas should include ophthalmic examinations every 12 months beginning in infancy or early childhood. Screening for RCC should include MRI scans of the abdomen every 12 months from age 16 years. Screening for pheochromocytomas should include blood pressure monitoring, annual blood and/or urine metanephrine testing and MRI scans.

Dr. Lam concluded by saying that VHL disease is a highly complex multisystem disorder that requires input from many different medical specialties. Coordination with and input from patients and their families is essential. Early diagnosis and regular surveillance can greatly improve prognosis.

**ELSTS AND VHL**

Samuel Gubbels, MD, Director of the UCHealth Hearing and Balance Clinics at UC Denver, presented on the relationship between endolymphatic sac tumors and VHL.

The endolymphatic sac is located in the back portion of the skull (posterior fossa), along the dural lining of the brain, and is part of the inner ear membranous system. It is less than 1cm in size, flat, fibrous and triangular in shape. Its function is to maintain endolymph homeostasis and remove waste.

Endolymphatic sac tumors (ELSTs) are a type of rare and slow growing tumor. While ELST have been reported as a cancerous type of tumor they do not spread to other places and are far less aggressive in their behavior than most malignancies. Rather, they are vascular and locally erosive. In people with VHL, they are thought to occur twice as much in females compared to males. They generally arise between the ages of 12-50 years, with an average age of diagnosis at about 30 years. 10-25% of people with VHL will develop ELSTs, with 30% of those occurring in both ears.

Symptoms from ELSTs may include hearing loss (progressive more often than sudden), ringing in ears, dizziness, ear fullness, facial weakness, headaches and other cranial nerve symptoms. It is important for people who are experiencing these symptoms to get a differential diagnosis to confirm that it is a VHL-related ELST. ELSTs are frequently misdiagnosed as Meniere’s Disease due to many of the same symptoms.

ELSTs can be diagnosed through the use of audiograms and imaging, including MRIs and CTs. Current screening guidelines for ELSTs in people with VHL call for audiology exams in infancy. Starting at age 5, MRIs of the posterior fossa and internal auditory canal should be performed every 2-3 years.

The main treatment for ELSTs is surgical resection. Hearing preservation is possible when dealing with small tumors and it is very important to make sure that the entire tumor is surgically removed. Surgery for ELSTs should include a neurootologist and neurosurgeon who are experienced in working with people who have VHL. It is usually an inpatient procedure, with an expected hospital stay of 2-3 days.

Some of the risks with surgery include dizziness, facial nerve problems, and hearing loss. Postoperative dizziness can be treated with vestibular therapy. There are a variety of procedures that can help with facial nerve problems, include rehabilitation. While standard hearing aids are not effective in general in patients who are experiencing ELST-related hearing loss, there are a number of other options, including CROS, or bone anchored hearing aids. Another option might be cochlear implants and routing hearing from both sides of the head to the functioning ear.

Dr. Gubbels concluded by emphasizing that screening and early detection are paramount when it comes to treating VHL-related ELSTs and preserving hearing.
Lauren Fishbein, MD, PhD, MTR, Assistant Professor of Medicine and Endocrinologist for the VHL Clinical Care Center at UC Denver, presented on VHL and the associated adrenal and pancreatic manifestations.

The adrenal glands and the pancreas are both endocrine glands. Endocrine glands are organs that produce hormones. Hormones are chemical messengers in the body that send messages about a particular function from one cell to another.

The adrenal glands produce several hormones, including adrenaline, that control energy, blood pressure, and metabolism. Adrenaline helps keep our blood pressure and heart rate up and controls our fight or flight response. Pheochromocytomas (pheos) are VHL-related tumors that occur in the adrenal medulla of the adrenal glands. About 10-20% of people with VHL will develop pheos. Symptoms of pheos may include high blood pressure, rapid heart rate, sweating, headache, anxiety, tremors, increased blood sugar, although some people with pheos have no symptoms. Paragangliomas (paras) are similar to pheos, except that they occur in nerve bundles outside of the adrenal glands. They are rare in people with VHL. Patients can be tested for pheos with a blood test that tests for plasma-free metanephrines and/or a 24-hour urine test that tests for urine fractionated metanephrines. If a person is found to have a pheo, they should be put on alpha blockers to block the effect of high adrenaline and control blood pressure, particularly before any type of surgery. Those with pheos are at risk for developing them in both adrenal glands. The optimal treatment is cortical-sparing surgical resection that preserve as much adrenal function as possible, preferably a partial adrenalectomy. However, cortical sparing surgery does carry a risk of the patient developing another pheochromocytoma in the remaining piece of adrenal gland. Adrenal insufficiency is caused by having no adrenal glands. Despite this, patients can still survive and thrive because all of the hormones produced by the adrenal glands can be replaced by medications.

The pancreas produces hormones that are involved in food breakdown and metabolism and controls signals for energy usage and stores. One of the primary function of the pancreas is the production of insulin, which helps control blood sugar by signaling the liver, muscle, and fat to use the sugar for energy. If there is a neuroendocrine tumor in the pancreas that produces high insulin levels, this can result in low blood sugar, confusion, vision changes, unusual behavior, rapid heartbeat, sweating, shakiness, and amnesia. The pancreas also produces glucagon, which makes sure that the body's blood sugar does not drop too low, by sending a message to the liver to make more sugar, as needed. Too much glucagon from a neuroendocrine tumor in the pancreas can cause blood sugar levels that are too high, resulting in diabetes, weight loss, blood clots, and more. Somatostatin is a hormone that, when produced in the pancreas, inhibits the secretion of other hormones and regulates the activity of the GI tract.

Having VHL increases the risk for several types of mostly benign pancreatic masses and cysts. Masses are solid, while cysts are fluid filled. One type of VHL-related mass is called a neuroendocrine tumor (pNET). About 12-17% of people with VHL will develop pNETs. The vast majority of pNETs in people with VHL are benign and non-functional. Guidelines suggest removal of pancreatic masses larger than 3cm, or with a doubling time of less than 500 days, in people with VHL. (Research by Dr. Amit Tirosh has shown that an exon 3 VHL mutation is another indicator for surgery, as it is associated with an increased risk for metastasis.) Patients can survive and thrive with a compromised, or a removed, pancreas by replacing the pancreatic hormones with medications. In this case, insulin would be a main hormone of concern when absent, which would cause diabetes mellitus. Other hormones and enzymes produced in the pancreas can also be replaced by medications.

Dr. Fishbein summarized by saying that early detection and treatment of VHL-related adrenal and pancreatic tumors, along with ongoing surveillance, can greatly improve patient prognosis when it comes to the endocrine-related manifestations of VHL.
VHL RESEARCH UPDATE

Ramaprasad Srinivasan, MD, PhD, Head of the Molecular Cancer Therapeutics Section of the Urological Oncology Branch at the NIH/National Cancer Institute, presented information on current research into VHL and what is in store for the future.

Currently, the management standard for most VHL-related tumors is local control, which usually means surgery or focal ablation. The goal is to minimize the risk of metastases, when applicable, as well as to control local symptoms and systemic complications. This is associated with significant lifetime morbidity, including complication from surgery, gradual loss of renal function, pancreatic or adrenal insufficiency, and neurological deficits.

An alternative to the local control method that is being explored is systemic therapy. The primary goals of this approach are to prevent tumor growth, reduce tumor size and prevent new tumors, thereby delaying surgery or avoiding all together. Other goals of systemic therapy include preventing distant metastasis, improving quality of life and preserving function with acceptable short and long term side effects. Increased understanding of the VHL–HIF pathway and the consequences of VHL gene mutation has led to the identification of a number of therapeutic targets for RCC. Some of the therapies under investigation that are inhibitors of angiogenesis/VEGFR include sunitinib, pazopanib and vandetanib. Some of the therapies under investigation that target HIF are 17AAG, PT2385, and PT2977.

Dr. Srinivasan summarized by stating that thus far, experience has been restricted to small, single arm, phase 2 studies. VEGFR and HIF are the primary targets being pursued with new systemic therapies. Clinical trials have shown tumor regression with VEGFR inhibitors, but patient tolerability is a significant issue and the long term clinical benefit is still unknown. HIF2 inhibitors offer a new avenue of investigation.

THE GENETIC SUBTYPING OF VHL

Alexandra Suttman, MS, CGC, a genetic counselor and instructor at Children’s Hospital Colorado, presented on the genetic subtyping of VHL.

VHL is a genetic disease that affects about 1 out of every 36,000 people. Almost all people with VHL will have symptoms by the age of 75 and most will have at least one symptoms by their 2nd or 3rd decade of life. Manifestations and symptoms of VHL can be variable, even among members of the same family. Most cases of VHL are inherited, although about 20% of cases are considered de novo, or first-in-family. The VHL gene is a tumor suppressor gene involved in cell communication pathways and in blood vessel formation. Harmful changes, or mutations, in the VHL gene can lead to accumulation of proteins that are typically degraded. These proteins instruct cells to continue dividing at a rapid pace, forming tumors. These tumors are typically benign, but can cause problems due to location and size. Some of the tumors associated with VHL are hemangioblastomas of the brain, spine and retinas, clear cell renal cell carcinoma (RCC), pheochromocytomas/paragangliomas (pheos/paras), pancreatic neuroendocrine tumors (pNETs), endolymphatic sac tumors (ELSTs) and cystadenomas of the epididymis (males) and broad ligament (females).

VHL mutations can be caused by spelling mistakes in the genetic code or by missing or extra genetic information. VHL is classified into 5 different subtypes based on how a mutation affects the protein. Different mutations can lead to different manifestations of VHL. Classification of VHL is primarily associated with presence or absence of pheos and then risk for RCC. Subtype of VHL is based on three unique categories of mutations. Truncating variants, or exon deletions, cause proteins to be only partially made.
These are also known as nonsense variants. Total gene deletions result in no protein being made. Missense variants result in a full protein being made, but with an altered composition.

A patient's VHL subtype can be determined by a physician or a genetic counselor based on their genetic test report. If no genetic testing had been done, subtype can be hypothesized based on personal and family medical history. When reading a genetic report, there are two values that are designated: a coding change and a protein change. The protein value correlates most with VHL subtype. The purpose of subtyping is to evaluate clinical risks and suspicion, as well as for research purposes. Every person with VHL, and their family members who also have VHL, have a genotype that is a unique identifier to them and their family.

Ms. Suttman concluded by saying that management of VHL is not currently based on subtype because patients may develop manifestations and symptoms that are outside of their subtype. More research into the relationship between VHL genotype and phenotype may yield valuable information in the future regarding relative risk and treatment/surveillance options.

### VHL IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS

Lindsey Hoffman, DO, MS, Assistant Professor of Pediatric Oncology and UC Denver VHL CCC Pediatrician, presented on VHL and its impact on children, adolescents and young adults.

VHL is an autosomal dominant disease, which means that all children of a person with VHL will have a 50% chance of inheriting the mutation. VHL is commonly passed down through families, with about 80% of cases being inherited. The other 20% of cases are known as de novo, or first-in-family. Often children are diagnosed very young, especially when they have a family member that is known to have VHL.

Research has suggested that approximately 70% of VHL patients will have manifestations before age 18. The most common manifestations at that age are retinal hemangioblastomas (about 34%) and CNS hemangioblastomas (about 29%). With regard to retinal hemangioblastomas, visual outcomes are significantly improved when the hemangioblastomas are detected before becoming symptomatic. Pancreatic cysts and pheochromocytomas are seen in about 20% and 40%, respectively, of VHL patients below the age of 18. No reproductive cystadenomas or ELSTs have been observed in people with VHL before the age of 18. Research has also shown that children with VHL develop about 0.4 new tumors per year, with the highest risk for new tumors between the ages of 30 and 34. People with VHL between the ages of 12 and 20 years have been shown to develop more CNS hemangioblastomas per year than those who are older.
“Until a cure is found, surveillance is a patient's strongest defense to prevent severe VHL complications.” The rationale for surveillance is that early detection and treatment will decrease morbidity and mortality. This surveillance should continue throughout a patient's life, regardless of age. Beyond medical imaging, surveillance includes maintaining a healthy level of suspicion based on signs and symptoms. The timing of intervention depends largely on tumor location, size, and rate of growth. Retinal lesions should be addressed right away. Kidney and pancreatic tumors should typically be addressed once they reach 3cm. CNS hemangioblastomas should be treated once they become symptomatic. In children, holding off on treatment/intervention unless symptomatic may be better given near certain need for intervention in adulthood.

Genetic testing should always be performed with the guidance and support of a genetic counselor. There should also be ongoing support to reinforce information, provide age-appropriate information and psychosocial support. If tested when young, patients are recommended to repeat formal genetic counseling in early to late teen years, as well as at the time of family planning.

Surveillance, especially on children, can be very scary. “Scanxiety” is well described around the time of surveillance imaging and may include fear of the scans themselves, fear of the findings, and/or fear of waiting between scans. Surveillance can provide powerful knowledge. Negative testing can provide relief. Creating a surveillance team that can provide psychological support can help to form trust and give the patient a solid support system.

Dr. Hoffman concluded by saying that the most common VHL manifestations in childhood are retinal hemangioblastomas, CNS hemangioblastomas and pheochromocytomas. While surveillance guidelines are becoming more evidence-based, strong relationships between genetic counselors, medical providers, patients and families is key to successful outcomes.

VHL AND NEUROSURGERY: SIDE EFFECTS OF THE DISEASE AND THEIR THERAPIES

Kevin Lillehei, MD, Director of the Neuro-Oncology Program, Chair of the Department of Neurosurgery and Member of the VHL CCC at UC Denver, presented on neurological manifestations of VHL, side effects and therapies.

Hemangioblastomas are tumors that very common in VHL patients and can be seen in the brain and spine. They are benign tumors that are classified as Grade 1 by the World Health Organization. Endolymphatic sac tumors (ELSTs) arising in the inner ear are also considered CNS manifestations.

In the brain, hemangioblastomas are usually found in the cerebellum and brainstem. Symptoms depend on location, tumor size, tumor bleeding, and swelling. Tumors in the cerebellum can bleed and block the flow of spinal fluid. This can result in nausea, loss of coordination, and tiredness. Brainstem lesions can cause difficulties in swallowing, breathing, seeing, and tiredness. Spinal lesions can cause weakness, balance issues, sensory symptoms, and bowel and bladder problems. The average age that VHLers first develop symptoms from these tumors is about 18-35 years old.

Since hemangioblastomas in the brain are benign, they are not in danger of spreading to other organs. However, they still can be dangerous. There is limited space in the skull and any tumor growth, swelling or cyst formation can greatly increase intracranial pressure causing symptoms. It should be noted that research has shown that most hemangioblastomas will grow in a “stuttering” manner, as opposed to a constant, progressive growth.

The vast majority of hemangioblastomas will remain asymptomatic and will never require treatment. Close surveillance with MRI scans of the brain and spine is advised. Surgery is the primary treatment option, particularly when dealing with symptomatic lesions. Surgical removal of non-symptomatic lesions is highly controversial and not generally recommended. When treated appropriately, excellent long-term outcomes
can be expected with surgery. In certain circumstances, stereotactic radiosurgery (SRS) is an emerging treatment option. Evidence has shown that SRS in the brain is much more effective for small and solid tumors, as compared to large and cystic tumors. Furthermore, SRS is often preferred for patients who are deemed high risk for surgery, those with multiple lesions, or those with tumors not amenable to surgical removal. SRS is still being researched and the long-term effects are not yet known. Dr. Lillehei concluded by saying that the standard treatment for brain and spine hemangioblastomas is surgical resection at the onset of symptoms. Patients who are vigilant with their surveillance and get the appropriate treatment at the right time can usually expect a very good prognosis.

RETINAL HEMANGIOBLASTOMAS: OPTIONS OF TREATMENT

Scott Oliver, MD, Chief of the Retina Service, Director of the Eye Cancer Program and Member of the VHL CCC at UC Denver presented on the retinal manifestations of VHL and the available treatment options.

Retinal hemangioblastomas are benign tumors that occur in the retinas of about 25-60% of people with VHL. In fact, they are the first manifestation to appear in about one third of VHL patients. These lesions are small and can be difficult to see. They are made up of blood vessels that can leak, which may lead to blurred vision and retinal detachment. Most of these lesions will occur in the peripheral retina. Blindness is rare, but can still occur, particularly without proper surveillance and treatment. Blindness is often the result of multifocal lesions and lesions at the optic nerve. Failure to properly address issues as they present can lead to recurrent retinal detachment.

Current guidelines call for those who have been diagnosed with VHL, or are at risk, to begin surveillance at birth. This will consist of a general screening by a pediatrician who will look for any signs of eye issues. Starting at age 1, patients should get an annual, dilated, eye exam. This exam should be performed by an ophthalmologist using an indirect ophthalmoscope, using maximum dilation, in order to get a good view of the entire retina. In addition to the dilated exam, some of the surveillance techniques that may be used are eye photography and fluorescein angiography.

Laser photocoagulation is the main treatment option used for retinal hemangioblastomas. This technique uses focused energy from a laser to cauterize the lesion. Repeat treatments are usually necessary. Another treatment option might be the use of anti-VEGF therapy, which may inhibit blood vessel growth and control leakage in the retina. It can offer the best visual outcome, but may require long term ongoing injections. In certain advanced cases, surgical resection may be another possible treatment option. Some therapies that are being explored include external beam radiotherapy, propranolol and sunitinib. Definitive regression can be achieved in some tumors using radiotherapy, however the side effect may limit vision.

Dr. Oliver summarized by saying that early detection of eye tumors is key and the treatment of small tumors is relatively straightforward using laser photocoagulation. Early, timely, and continuous periodic retinal examination by a retinal specialist with knowledge of VHL can prevent vision loss.

VHL AND THE KIDNEY

Adam Metwalli, MD, Chief of the Division of Urology at Howard University Hospital and Director of Urologic Oncology at Howard University Cancer Center, discussed the detection and treatment of VHL-related tumors in the kidneys.

VHL manifestations in the kidneys can include solid tumors, complex cysts and simple cysts. Research has shown that renal cell carcinoma (RCC) related to hereditary disorders, like VHL, comprise about 4% of all RCC cases. About 25-60% of people with VHL will develop RCC, usually with multiple tumors in both kidneys. The onset of VHL-related RCC generally occurs earlier than the onset of RCC in those without VHL. Studies
have shown that the median growth rate for VHL-related kidney tumors is about 3.7mm per year, with the fastest growth rate experienced by young males. There is a higher risk for metastases in tumors with higher diameter growth rates.

Renal tumors are addressed in several ways. The goals for managing kidney tumors in VHL patients are to minimize risk of kidney cancer metastasis, preserve renal function, minimize the total lifetime number of surgeries, and to monitor small lesions until they reach 3cm. Research has shown that metastases of RCC is highly unlikely in those with tumors smaller than 3cm. Active surveillance allows for the identification of troublesome tumors. When they meet the criteria for surgical removal, partial nephrectomy is recommended, in order to preserve kidney function. Radical nephrectomy should be avoided, if possible. There are a variety of surgical approaches for partial nephrectomy including traditional open incisions, as well as laparoscopic and robotic-assisted procedures. Surgery should be followed by a post-op renal function test.

Dr. Metwalli concluded by saying that the proper surveillance and treatment of VHL-related kidney tumors is of paramount importance. The best approach is a nephron sparing one, with a partial nephrectomy once the largest tumor reaches 3cm. This effectively “resets the clock” and provides the patient with the best chance for a long term positive outcome.