It has been nearly a year since I was diagnosed with VHL. After conquering my first radiation treatment in October, I have finally come to terms with my new reality. The next step in my journey is to use my story to help find a cure. As with any rare disease, the more information on patients, the better. That is why I have started the process of filling out the surveys on MyVHL (vhl.org/MyVHL).

MyVHL is a database that helps researchers identify patterns across those who have been diagnosed with VHL. Due to its rarity, there is not a lot of information out there. The surveys aim to help patients, researchers, and care providers better understand the condition. The information from these confidential, secure, and personal series of surveys will never be shared with anyone and our personal identity will remain safe and secure. We are assured to remain anonymous and safe. Per the MyVHL website, the data that individuals provide “helps researchers identify and uncover factors that may increase risk, inhibit or slow tumor growth, or lead to an effective cure.”

I was aware from conversations with the VHL Alliance staff that documenting my health in the surveys might be long and tedious. There would be information I might not know and would need to investigate. I also know just how important it is to share my VHL history because it could help another patient down the line. Now that I’ve started the process, I’m here to share my experience in hopes that it encourages others to do the same.

Filling out the surveys will be different for every patient. Depending on your medical history, for some it will be more time consuming than for others. While some people may require information from doctors or parents to complete the surveys, others may be able to complete them on their own. It is a good idea to collect as much information as you can before you start to attack the surveys. My suggestion is to begin with the areas where you haven’t had any issues, as those will be easiest for you to fill out.

I am lucky for a VHL Warrior. I currently only have one tumor near my spine, along with several cysts in my pancreas. Other patients, like my father, have had numerous tumors in different places. For these Warriors, it means filling out the surveys will be a longer process. But don’t let that deter you. The payoff in the end is worth it!

With a disorder like VHL, there is always a tinge of loneliness. There are not many of us and not many people can relate to what we are going through. That is why I liked how after each survey, it provided you a breakdown of what other people who participated reported. It was a graphical representation of the fact that we are not alone.

continued on page 2
JOIN ME IN PARTICIPATING IN MYVHL
continued from page 1

One of the questions I am plagued with most in this battle, and I’m sure a lot of others are as well, is “what can I do?” Filling out the MyVHL surveys is something we can each do. We can’t predict or control what VHL will do to our bodies, but we can do everything in our power to help find a cure. The first step is to share our story. Please join me in participating at vhl.org/MyVHL.

Clinical Trial Recruitment

PT2977-202: An open-label phase 2 study to evaluate PT2977 for the treatment of von Hippel-Lindau disease-associated renal cell carcinoma

More information can be found at: vhl.org/clinical-trials or clinicaltrials.gov
(Study Number NCT03401788), or VHL Alliance: josh.mann@vhl.org, 617.277.5667 x4

Now Enrolling at

Huntsman Cancer Institute
Massachusetts General Hospital
National Institutes of Health/National Cancer Institute
University of Michigan Medicine
University of Pennsylvania
University of Pittsburgh Medical Center
UT MD Anderson Cancer Center
UT Southwestern Medical Center
Vanderbilt University
Yale University Medical Center
Aarhus University Hospital, Denmark

Study sponsor: Peloton Therapeutics, Inc.

HAPPIENGS

VHLentines
Honor your healthcare professional this Valentine’s Day by sending them a VHLentine.
Sign Up Now: vhl.org/VHLentine

Michigan Annual VHL Meeting
Saturday, April 13th
Ann Arbor, MI

NYC VHL Patient and Family Meet Up
Saturday, April 17th, 8:30 AM - 1 PM
Hosted by the Columbia/New York Presbyterian VHL Comprehensive Clinical Care Center, New York, NY

Mom’s Day Run
Sunday, May 12th
Ventura Beach, CA

Young Adult Retreat
Friday, June 14th - Sunday, June 16th
Boston, MA

For more information visit vhl.org/events

May Awareness Month
What are you doing to promote VHL Awareness?
Contact Heidi at heidi.leone@vhl.org for help or ideas or look on Pinterest pinterest.com/VHLAlliance
by Eric Jonasch, MD, VHLA Board Member, Chair of Clinical Advisory Council and Research Council

It was an honor to host the 13th International VHL Medical/Research Symposium at The University of Texas MD Anderson Cancer Center in Houston. The meeting included three packed days of cutting-edge advances in VHL research, as well as multiple lively debates designed to improve clinical care.

Reevaluating the current active surveillance guidelines (vhl.org/screening-guidelines) was one of the topics discussed. A recent medical publication by Dr. Rednam, et al., indicates that perhaps it is wise to initiate MRI screening at an earlier age. Are we missing developing lesions? If so, what could be the medical impact? What would be the cost/benefit of scanning at an earlier age and would these scans be covered by insurance? To help resolve these questions, Dr. Anthony Daniels at Vanderbilt University Medical Center is leading a task force comprised of experts in each relevant medical specialty. This group will evaluate whether or not the screening guidelines should be changed and, if so, how. Ultimately, the final guidelines will be shared with the VHL community, as well as the various medical societies.

A recurring theme during the course of the symposium was the importance of the MyVHL: Patient Natural History Study (vhl.org/MyVHL). While a number of clinical researchers maintain their own natural history studies based on the patient population seen at their institutions, data amassed through MyVHL is invaluable for better understanding VHL, linking research to clinical manifestations, advancing clinical trials, and reaching VHLA’s vision of Curing Cancer through VHL.

MyVHL data are already enlightening us. For example, 40% of patients describe issues with digestion, 25% experience panic attacks, 24% suffer persistent headaches, and 21% noted thyroid issues. All of these numbers are greater than those found in the general population. Are these medical issues directly related to the VHL gene mutation? A consequence of VHL manifestations? Or a side effect of surgery or scanning? Only your data can answer these questions!

For those of you who may have concerns about this important online study, I can assure you that your data are safe, secure, and confidential. NO identifiable data will be shared with ANYONE (not even me)! Your data are safeguarded using similar processes used by hospitals around the world. Under NO condition will your data be sold or shared with an insurance company of any kind! I strongly recommend you visit the MyVHL Promise Statement at vhl.org/MyVHL-wepromise.

With this in mind, I appeal to each and every VHL patient to participate in MyVHL and remember, it is a longitudinal study, meaning we ask that you revisit MyVHL at least once a year to update your data. Your participation is the key to a cure.

We need you in our quest to find a cure for VHL. Help us Help you!

<table>
<thead>
<tr>
<th>Medical Issue</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digestive complaints</td>
<td>40.4%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26.3%</td>
</tr>
<tr>
<td>Panic attacks</td>
<td>25.3%</td>
</tr>
<tr>
<td>Persistent headaches</td>
<td>24.2%</td>
</tr>
<tr>
<td>Thyroid Issues</td>
<td>21.2%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18.2%</td>
</tr>
<tr>
<td>Nervous system complaints</td>
<td>17.2%</td>
</tr>
<tr>
<td>Persistent hiccups</td>
<td>13.1%</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>13.1%</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>8.1%</td>
</tr>
<tr>
<td>Cardiovascular complaints</td>
<td>7.1%</td>
</tr>
<tr>
<td>Stroke</td>
<td>7.1%</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>5.1%</td>
</tr>
<tr>
<td>Respiratory complaints</td>
<td>5.1%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>4.0%</td>
</tr>
<tr>
<td>Heart Attack</td>
<td>3.0%</td>
</tr>
<tr>
<td>Coronary artery Disease</td>
<td>3.0%</td>
</tr>
<tr>
<td>Parathyroid Issues</td>
<td>2.0%</td>
</tr>
</tbody>
</table>
The 13th International VHL Medical/Research Symposium held in Houston, TX on October 4-6, brought together VHL researchers, clinicians, and patients from around the world. The symposium was a great way for researchers to have the opportunity to meet and interact with physicians treating VHL and with VHL patients and families. Most importantly, it was a venue to discuss the tremendous advances that have been made in research that are bringing us closer to more effective treatments for VHL.

An entire day was devoted to presentations and discussions directed to VHL patients, their families, and friends. In addition to lay summaries from the previous two days, data from MyVHL, and VHL Alliance programs, including support groups, CCC Process Improvement, and Wellness Coaching were discussed.

Three major outcomes from the symposium are:

• Form a task force to reevaluate VHL Surveillance Guidelines and determine any necessary changes
• Identify additional data and tools needed to assess the feasibility of genetic therapy for VHL retinal eye disease
• Publish meeting outcome summary in Clinical Cancer Research (CCR) Journal

For presentation slides, video recordings, and written summaries of the presentations from the symposium visit: vhl.org/about/resources/13th-international-vhl-medical-symposium

Evolution of Clinical Studies in VHL Disease
Ramaprasad Srinivasan, MD, PhD, National Institutes of Health, National Cancer Institute

Patients with VHL are at risk for developing tumors in multiple organs, including the kidney (clear cell renal cell carcinoma), the pancreas (pancreatic neuroendocrine tumor), pheochromocytomas, CNS hemangioblastomas, and retinal hemangioblastomas. VHL associated tumors are managed surgically in most organ systems affected, with tumors resected periodically. The goal of surgery is to minimize the risk of metastases and to control local symptoms and systemic complications. Since repeated surgeries are associated with significant long term morbidity, there is significant interest in the development of nonsurgical approaches for VHL patients.

VHL is caused by germline mutations in the VHL tumor suppressor gene. One of the better characterized consequences of loss of VHL function is the dysregulated expression of hypoxia inducible factors, particularly HIF-2 alpha, and consequent overexpression of growth factors such as Vascular Endothelial Growth Factor (VEGF) and Epidermal Growth Factor Receptor (EGFR).

A variety of approaches targeting the downstream consequences of VHL inactivation have been evaluated in the clinic. While approaches targeting the VEGF-axis are associated with antitumor activity, the toxicity profile is not tolerable to many VHL patients and the long term clinical utility of these approaches remains unclear. More recently, approaches targeting HIF-2 alpha have attracted significant interest and are currently undergoing clinical evaluation in VHL patients.

Universal Reflex Referral to VHL
Comprehensive Clinical Care
Center of Patients Presening to Ophthalmologist Leads to Dramatic Improvement in Guideline-Concordant Screening: Results of a Pilot Study
Anthony Daniels, MD, Vanderbilt University School of Medicine and VHL CCCC

VHL affects many organ systems and requires treatment by multiple specialists. Thus, care is often fragmented. It is difficult for a physician seeing a VHL patient for the first time to ascertain which other specialists are ordering screening studies, and whether the patient’s screening is up-to-date.

“The evidence suggests that the simple intervention of implementing a universal reflex referral policy for VHL patients to a CCCC, dramatically improved guideline-concordant screening rates to 100%.”

continued on page 5
date and guideline-concordant. In 2017, Vanderbilt became one of a dozen Comprehensive Clinical Care Centers (CCCCs) in the U.S. At that point, the hospital instituted a quality improvement initiative to improve guideline-concordant screening. All VHL patients who came to their ophthalmology clinic were referred directly to the Vanderbilt CCCC oncologist for surveillance imaging. This was done regardless of whether they were being followed by other specialists.

The data collected shows that prior to creating the CCCC in 2017, 0% of patients were guideline-concordant at the time they presented to ophthalmology, while only 29% were concordant afterwards. After creating the CCCC and the reflex referral initiative, rates of guideline-concordant surveillance imaging increased to 100%, following the reflex referral. The data also showed that 50% of patients referred from ophthalmology to CCCC oncology had (non-ocular) tumors requiring intervention at the time of initial screening imaging.

Rates of guideline-concordant screening have historically been poor, even for patients being followed for VHL-related tumors by subspecialists. The evidence suggests that the simple intervention of implementing a universal reflex referral policy for VHL patients to a CCCC, dramatically improved guideline-concordant screening rates to 100%. Half of all patients have a (non-ocular) tumor requiring treatment at the time they present to ophthalmology, underscoring the importance of expeditious referral.

CCC CORNER

The VHL Alliance is pleased to recognize Henry Ford Hospital in Detroit, MI as the newest VHL Clinical Care Center and Sheba Medical Center in Ramat Gan, Israel as the newest International VHL Clinical Care Center. The VHL team at Henry Ford is led by Dr. Craig Rogers and the VHL team at Sheba is led by Dr. Amit Tirosh.

Dr. Rogers is a urologist specializing in robotic surgery for kidney cancer, prostate cancer, adrenal tumors, testis cancer, penile cancer, and bladder cancer. Dr. Rogers trained at some of the top medical centers in the country and has learned alongside the pioneers of these techniques. He completed a Urologic Oncology Fellowship at the National Cancer Institute, NIH in Bethesda, MD working with VHL, BHD, and HLRCC patients. He has extensive experience offering robotic partial adrenalectomy for adrenal sparing option when indicated for VHL patients with pheochromocytoma. Dr. Rogers and his team are committed to working closely with the VHL Comprehensive CCC at UMichigan to care for and address the needs of Michiganders all over the state and region. If you are interested in pursuing care at Henry Ford Hospital, you can reach out to the team's Point of Contact (Arleeta Ellerbee) by phone at: 313.916.5362 or by email at: aellerb1@hfhs.org.

Dr. Tirosh is an endocrinologist with a specialty in the management of VHL-related neuroendocrine tumors (pNETS). He completed a fellowship at the National Insitutes of Health and has written several key publications in the field and is active in VHL-related translational and genetic research. Dr. Tirosh leads a bioinformatics lab with focus on endocrine manifestations of VHL and other hereditary syndromes. If you are interested in pursuing care at Sheba Medical Center, you can reach out to Dr. Tirosh by phone at: +972.50.6844706 or by email at: amit.tirosh@sheba.gov.il.

We are also excited to announce the restructuring of the VHL Clinical Care Center at UCLA, with the addition of Dr. Brian Shuch, previously the Sponsor of the CCC at Yale Medical Center, joining the team. We are pleased that Dr. Sandy Liu and Dr. Shuch have put together a team of VHL-experienced clinicians who are ready to provide expert surveillance, treatment, and care to all VHL patients in the Southern California and beyond.

Do you or your family members with VHL receive care at a VHL Clinical Care Center? If so, we want to hear from you! We invite you to submit any feedback that you have about your experience at vhl.org/cccfeedback. You are welcome to remain anonymous. Your feedback is important to helping us improve the quality of care for all.
The 2018 VHL Alliance Annual Meeting was held in Denver, CO. The agenda included nine scientific presentations, patient and caregiver break-out sessions focusing on the emotional aspects of VHL, and a panel discussion demonstrating how a VHL multi-system medical condition is handled at a CCC. Below we highlight two of the presentations.

For presentation slides, video recordings, and written summaries of the presentations from the annual meeting visit: vhl.org/about/resources/annual-meeting-presentations.

VHL in Children, Adolescents, and Young Adults

Lindsey Hoffman, DO, MS, Assistant Professor of Pediatric Oncology and UC Denver VHL CCC Pediatrician

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.

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.

Endocrinology and VHL: The Adrenals and the Pancreas

Lauren Fishbein, MD, PhD, MTR, Assistant Professor of Medicine and UC Denver VHL CCC Endocrinologist

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

continued on page 7
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 functions 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.

Calling all Young Adults for the 2019 Young Adult Retreat

Ages 18-32
June 14 -16, 2019
Boston, MA

Learn more at vhl.org/YAR
MyVHL:
The VHL Patient Natural History Study

Do you want to help find a cure?

PARTICIPATE NOW!!

vhl.org/MyVHL

Learn more about your VHL and contribute to finding a cure. And, when you complete the surveys and upload your scans (or submit a Records Release Form), you will be eligible to receive a $50 Amazon gift card (US-based participants only). All of the information shared in MyVHL will remain secure and confidential.