



20 **VHL Annual Family Weekend** 20
Hosted by Huntsman Cancer Center, Salt Lake City, UT



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Important Resources

PUBLICATIONS

The VHL Handbook: What You Need to Know about VHL: Version 6, Revised 2020

A reference handbook for people with von Hippel-Lindau, their families, and support personnel

VHL Handbook Kids Edition: Handbook for Parents & Kids Living with VHL:

Written by a team of parents and professionals and illustrated by kids with VHL, the book is upbeat and hopeful, helping children understand VHL and how to manage their health.

Visit vhl.org/handbook

VHL Patient Vignettes: Personal stories, thoughts, and tips submitted by people dealing with the diagnosis of von Hippel-Lindau

This and other items can be purchased at vhl.org/store

WEBSITE RESOURCES

Suggested Surveillance Guidelines 2020: Until a cure is found, active surveillance is a patient's strongest defense to prevent severe VHL complications. vhl.org/surveillance-guidelines

Clinical Care Centers: vhl.org/ccs

SUPPORT

Monthly Telephone Discussion Calls: vhl.org/calls

Patient/Caregivers Call: vhl.org/ptcgcall

Parents Call: vhl.org/parentscall

VHL Low/No Vision Call: vhl.org/lownovisioncall

Mentor Program: Call 617.277.5667 x4 or e-mail info@vhl.org for more information.

Toll-free Hotline: Call 800.767.4845 x1

VHLApp for iOS: vhl.org/VHLApp. Android version coming soon.

On-line Support:

VHLA Facebook Page: facebook.com/VHLAlliance

VHLA Private Facebook Discussion Group: facebook.com/groups/VHLawareness

VHL Caregiver Connection: facebook.com/groups/vhlcaregivers

VHL: Parents to Parents: facebook.com/groups/VHLparents2parents

VHL Low/No Vision Facebook Group: facebook.com/groups/vhlvision

DONATE

The VHL Alliance depends on your donations to continue to fund research, education, and support. VHLA envisions Curing Cancer through VHL vhl.org/donate.

2020 Annual VHL Family Meeting

October 24, 2020

Agenda

NOTE: All times are Eastern times

10:00 AM	Introduction and Welcome	<i>Samantha Greenberg, MS, CGG:</i> Huntsman Cancer Institute, VHL CCCC Point of Contact <i>Chandra Clark:</i> Executive Director, VHL Alliance
10:15 AM	VHL 101	<i>Kristen Pauley, MS, CGC:</i> Huntsman Cancer Institute
10:45 AM	Living with VHL: Coping with the Diagnosis and Medical Management	<i>Yelena Wu PhD:</i> Assistant Professor, Department of Dermatology Huntsman Cancer Institute Investigator
11:15 AM	The Emotional Roller Coaster of VHL: <i>Separate Breakout Sessions for Patients and Caretakers</i> Patients: Psychosocial challenges faced by patients with VHL and techniques to manage them Caregivers: Psychosocial challenges faced by caregivers of patients with VHL and techniques to manage them	<i>Leona deVinne, CPCC, ACC:</i> Accendo Consulting; VHL Alliance <i>Rod Miller, MBA, CPHR MHCS:</i> Trained & Certified Life Coach
12:15 PM	Urological Findings in VHL	<i>Alejandro Sanchez, MD:</i> Assistant Professor in the Division of Urology, University of Utah School of Medicine; Huntsman Cancer Institute Investigator
12:45 PM	VHL and Brain Tumors: Bench to Bedside	<i>Randy Jensen, MD, PhD:</i> Brain Tumor Research Team at Huntsman Cancer Institute
1:15 PM	Lunch Break	

NOTE: All times are Eastern times

1:45 PM	VHL and Endocrine Tumor Susceptibility	<i>Heloisa Soares, MD</i> : NET Program, Huntsman Cancer Institute
2:15 PM	Retinal Findings in VHL	<i>Eric Hansen, MD</i> : Assistant Professor of Ophthalmology and Visual Sciences, Moran Eye Center, University of Utah Health
2:45 PM	Radiology Imaging	<i>Glen Morrell, MD, PhD, MPHE</i> : Associate Professor of Radiology at the University of Utah Health System
3:15 PM	Screening Guidelines	<i>Othon Iliopoulos, MD, PhD</i> : Associate Professor, Medicine, Harvard Medical School; Associate Professor of Medicine, Center for Cancer Research, Massachusetts General Hospital
3:45 PM	Break	
4:00 PM	Screening Adherence in Adolescents and Emerging Adults	<i>Samantha Greenberg, MS, CGG</i> : Huntsman Cancer Institute, VHL CCCC Point of Contact
4:30 PM	State of VHLA: 2020	<i>Camron King</i> , Chair, VHLA Board of Directors
4:45 PM	Research Update	<i>Mei Koh, PhD</i> : Assistant Professor of Pharmacology and Toxicology, University of Utah School of Medicine
5:15 PM	Clinical Trial Update	<i>Benjamin Maughan, MD, PharmD</i> : Assistant Professor in the Division of Medical Oncology, Huntsman Cancer Institute
5:45 PM	Concluding Remarks	<i>Chandra Clark</i> : Executive Director, VHL Alliance
6:00 PM	Adjourn	

2020 Annual VHL Family Meeting

October 24, 2020

Conference Speakers

Kristen Pauley, MS, CGC

Huntsman Cancer Institute, VHL CCCC Point of Contact



Kristen Pauley is a board-certified and licensed genetic counselor with a master's degree in genetic counseling from Thomas Jefferson University. She received her bachelor's degree from Villanova University in Biology. Ms. Pauley began working at Huntsman Cancer Institute in June 2019. She provides genetic counseling regarding hereditary cancer risks to patients in the Family Cancer Assessment Clinic. She also provides genetic counseling for hereditary conditions with increased risks for renal cancer such as von Hippel-Lindau (VHL) to patients and families.

Ms. Pauley's research interests include genetic education, alternative genetic counseling models/methods, and genetic testing modalities. She is also involved in the University of Utah Graduate Program in Genetic Counseling (UUGPGC). She teaches and provides clinical supervision at Huntsman Cancer Institute for UUGPGC students.

Yelena Wu PhD

Assistant Professor, Department of Dermatology Huntsman Cancer Institute Investigator

Dr. Yelena Wu is a child health psychologist. She is a faculty member at the University of Utah in the Department of Dermatology and Huntsman Cancer Institute. Dr. Wu is a clinician within the Family Cancer Assessment Clinic at Huntsman Cancer Institute where she works with children and families who have a genetic predisposition to developing cancer. Her research focuses on skin cancer prevention among at-risk pediatric populations, including within families and in the school setting.



Leona deVinne, CPCC, ACC

Accendo Consulting; VHL Alliance



Leona deVinne is a VHL patient and caregiver and knows the impact of the disease first hand. Leona is a Professional Certified Coach and facilitates the VHL monthly Patient/Caregiver and Parents calls. She recently developed the VHL Medical Coaching program to provide VHL Medical practitioners with a very robust skill set to support VHL patients more fully. She is a firm believer that we are all here for a reason and that it is not so much what happens to us in our lives, but rather what we do despite life's challenges, that has the most meaning and impact.

Rod Miller, MBA, CPHR MHCS

Certified Leadership & Executive Coach

Rod Miller is NFP executive leader with experience in a variety of sectors and industries. Recognized for his transformative leadership, business development, and ability to develop exceptional organizations. In his work Rod has developed and launched innovative biopharmaceutical products in Canada to help underserved patient populations, he has travelled the globe developing and implementing workforce capacity building projects supporting the development of human potential locally to serve international development needs. Over the course of his career Rod has developed experiences in academia, business development, sales & sales leadership, marketing, and general operations.



Rod holds undergraduate degrees in zoology and economics. In addition, he holds a MBA in leadership and strategy from the University of Calgary Haskayne School of Business. As a lifelong learner Rod has also pursued studies in human centered design. Rod is a Chartered Professional in Human Resources, the Canadian standard for exceptional human resources practices.

Over the course of his career Rod has held board positions in the areas of community development and engagement, social support for children, and with professional associations. As a caregiver and board member, Rod is committed to the work of the VHL Alliance and looks forward to working with the board, staff, and volunteers to not only bettering the quality of life for patients and families but to also move toward a cure for VHL.

Alejandro Sanchez, MD

*Assistant Professor in the Division of Urology, University of Utah School of Medicine;
Huntsman Cancer Institute Investigator*



Dr. Alejandro Sanchez received his undergraduate degree from the University of Florida where he graduated Summa Cum Laude in Biochemistry. He earned his medical degree from Harvard Medical School and completed his urologic surgery training at Massachusetts General Hospital. Dr. Sanchez then completed a fellowship in urologic oncology at Memorial Sloan Kettering Cancer Center where he received a Young Investigator Award from the American Society of Urologic Oncology to evaluate the mechanisms underlying the association of sarcopenia (low skeletal muscle mass) and poor oncologic outcomes in patients with clear cell renal cell carcinoma. During his fellowship, Dr. Sanchez also received the Chairman's Award for Excellence in Basic Science.

As an Assistant Professor in the Division of Urology at the University of Utah School of Medicine and Huntsman Cancer Institute, Dr. Sanchez's research efforts are primarily focused on clinical trial development and translational research with a primary interest in renal cancer. Dr. Sanchez is also the co-leader of the VHL/high-risk renal cancer clinic at Huntsman Cancer Institute.

Randy Jensen, MD, PhD

Brain Tumor Research Team at Huntsman Cancer Institute

Dr. Randy Jensen specializes in brain tumor surgery. He has a particular emphasis using preoperative imaging, intraoperative navigation, intraoperative cortical mapping and intraoperative MRI to maximize tumor resection and minimize surgical complications. He treats patients with malignant, benign, and metastatic brain tumors. He has many clinical trials for patients with brain tumors and has a laboratory effort examining brain tumor biology. He is also a member of the Brain Tumor Research Team at Huntsman Cancer Institute.



Heloisa Soares, MD

NET Program, Huntsman Cancer Institute



Dr. Heloisa Soares is a medical oncologist with a focus in GI cancers and neuroendocrine tumors. She is an assistant professor at the Huntsman Cancer Institute (HCI) at University of Utah. Dr. Soares received her medical degree at Faculdade de Medicina do ABC in Brazil, where she was born. She completed her residency training at the Mount Sinai Medical Center of Florida and her hematology-oncology fellowship training and PhD in molecular biology at UCLA. Dr. Soares has neuroendocrine tumors, and gastrointestinal (GI) cancers as the major focus of her research and clinical activities. She serves as the co-physician leader in the GI Clinical Trials Research Group at HCI. In 2019, became a member of the board of directors for The North American Neuroendocrine Tumor Society (NANETS). Additionally, she is a member of the NCI NET taskforce and member of SWOG and NRG cooperative groups. Dr. Soares is a passionate advocate to patients and has, along many other patient-centered activities, volunteered at the ASCO Advocacy Summit on Capitol Hill and had the opportunity to meet members of congress and advocate to improve patient care. You can follow her on twitter as @helops79.

Eric Hansen, MD

Assistant Professor of Ophthalmology and Visual Sciences, Moran Eye Center, University of Utah Health

Dr. Eric Hansen is an Assistant Professor of Ophthalmology and Visual Sciences at the University of Utah and Vitreoretinal Specialist at the Moran Eye Center. He completed his residency in Ophthalmology at Bascom Palmer Eye Institute in Miami, FL, a Global Ophthalmology fellowship and a vitreoretinal fellowship at the University of Utah. Dr. Hansen is currently training with two prominent ocular oncologists, Dr. J. William Harbour and Dr. Zelia Correa, at Bascom Palmer in order to build an ocular oncology service at the University of Utah.



Glen Morrell, MD, PhD

Department of Radiology, Huntsman Cancer Institute



Dr. Glen Morrell is Associate Professor of Radiology at the University of Utah Health System. His clinical area of expertise is imaging of the abdomen and pelvis, including CT, ultrasound, and MRI. Dr. Morrell is the radiology liaison to the VHL Comprehensive Clinical Care Center at the Huntsman Cancer Institute, which is associated with the University of Utah. Dr. Morrell obtained MD and PhD degrees from Stanford University. His PhD work was in Electrical Engineering developing new methods for MRI. His current research projects include sodium MRI of breast cancer and functional MRI of the human placenta.

Othon Iliopoulos, MD, PhD

Associate Professor, Medicine, Harvard Medical School; Associate Professor of Medicine, Center for Cancer Research, Massachusetts General Hospital

Dr. Othon Iliopoulos is an oncologist at Massachusetts General Hospital, where he serves as the Clinical Director of the VHL Disease/Familial Renal Cell Cancer Program. He is also an Associate Professor of Medicine at Harvard Medical School and at the Center for Cancer Research at MGH. Dr. Iliopoulos is a VHL Alliance Research Grant Recipient and is a Clinical Investigator for the MK-6482 (formerly PT-2977) clinical trial. His lab is involved in research pertaining to the main mechanisms underlying the reprogramming of cancer cell metabolism and cancer angiogenesis with the goal to develop mechanism-based strategies for selectively killing cancer cells. Dr. Iliopoulos is the Chair of the Clinical Advisory Council and the Research Council.



Samantha Greenberg, MS CGG

Huntsman Cancer Institute, VHL CCCC Point of Contact



Samantha Greenberg is a genetic counselor at Huntsman Cancer Institute. She received her Masters' from the University of Michigan for genetic counseling and public health after teaching seventh grade science in Tulsa, Oklahoma. Samantha oversees the von Hippel-Lindau (VHL) Care Center, Paraganglioma clinic, and high risk prostate clinic at HCI alongside a multidisciplinary team. Her research and interests center around VHL, prostate cancer, paraganglioma/pheochromocytoma, and education, where she serves as a faculty member with the University of Utah Genetic Counseling Program.

Camron King

Chair, VHLA Board of Directors

Camron King is President and Founder of Oakwood Strategic LLC. Recognized for his dynamic leadership, effective management and forward-thinking approach to brand building, Camron has been fortunate to have built a successful career in luxury value-added agriculture in both wine and caviar. His experiences are diverse ranging from marketing, public relations, management to government affairs. He is a regularly invited presenter at conferences and events around the world.



Camron attended Cal Poly, San Luis Obispo studying Environmental Horticultural Sciences; California State University, Sacramento studying Government and then graduate studies in Public Policy and Administration. Living in California his whole life, Camron is deeply committed to the tenets of the California lifestyle – great food, wine, and a healthy, balanced lifestyle.

Mei Koh, PhD

Assistant Professor of Pharmacology and Toxicology, University of Utah School of Medicine



Dr. Mei Koh is Assistant Professor of Pharmacology and Toxicology at the University of Utah. She joined the University in 2017 with two R01 grants funding research on the HIFs in kidney cancer. Dr. Koh holds a PhD in Molecular Pharmacology from the University of Manchester (UK) and completed her postdoctoral training at the Arizona Cancer Center. She has held faculty positions at the University of Texas M.D. Anderson Cancer Center and at the Sanford Burnham Prebys Medical Discovery Institute.

She is also founder and CEO of Kuda Therapeutics, a biotechnology startup developing novel therapies for kidney cancer.

Benjamin Maughan, MD, PharmD

Assistant Professor in the Division of Medical Oncology, Huntsman Cancer Institute

Benjamin Maughan MD, PharmD is an Assistant Professor in the Division of Medical Oncology at Huntsman Cancer Institute specializing in genitourinary malignancies. Dr. Maughan completed his PharmD, cum laude, from Idaho State University in 2004, then completed an oncology pharmacy residency at Mountain States Tumor Institute in 2005. Dr. Maughan earned his MD, cum laude, from the University of Kentucky, College of Medicine in 2010. He finished his Internal Medicine residency training with the University of Utah in 2013 and subsequently completed his medical oncology fellowship at Johns Hopkins in 2016. He has been awarded the Huntsman Cancer Institute Translational Scholar Award in 2019, and was selected for the 2019 SWOG Young Investigator Training Course.



Dr. Maughan has clinical and research interests in all genitourinary oncology, with a particular focus on the development of novel therapeutics and in identification of predictive biomarkers. During fellowship he studied predictive biomarkers in metastatic prostate cancer, specifically the role of truncated androgen receptors (AR-V7 expression) and loss of tumor suppressors (PTEN and Rb). More recently he is studying predictive biomarkers to immune therapy combinations in kidney, bladder, and prostate cancers. He is exploring novel immune therapy combinations including checkpoint inhibitors combined with radiation therapy (radium-223), oncolytic viruses (MVA-brachyury) and targeted therapies (such as cabozantinib).

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VHL 101

Kristen Pauley, MS, CGC

VHL 101

Kristen Pauley, MS, CGC
Licensed Genetic Counselor
Huntsman Cancer Institute



Overview

- Von-Hippel-Lindau (VHL)
 - What is VHL?
 - What are the signs/symptoms?
 - How is VHL inherited?
 - What's new and exciting with VHL?



What is Von-Hippel-Lindau

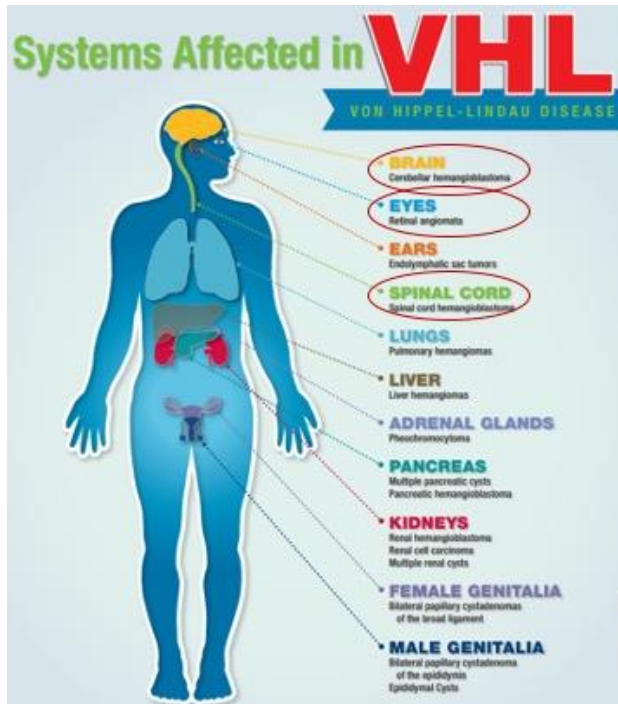
- A genetic condition characterized by tumors that grow along blood vessels in various different parts of the body
 - Benign or cancerous
- Due to a mutation (change) in the *VHL* gene
- Features of the condition can occur in childhood, adolescence or adulthood
- 80-97% of people with VHL have at least one finding by 65
- VHL presents differently in every person (even within the same family)

van Leeuwen RS, Ahmad S, Links TP, et al. Von Hippel-Lindau Syndrome. 2000 May 17 [Updated 2018 Sep 6]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from:



Signs and Symptoms of VHL



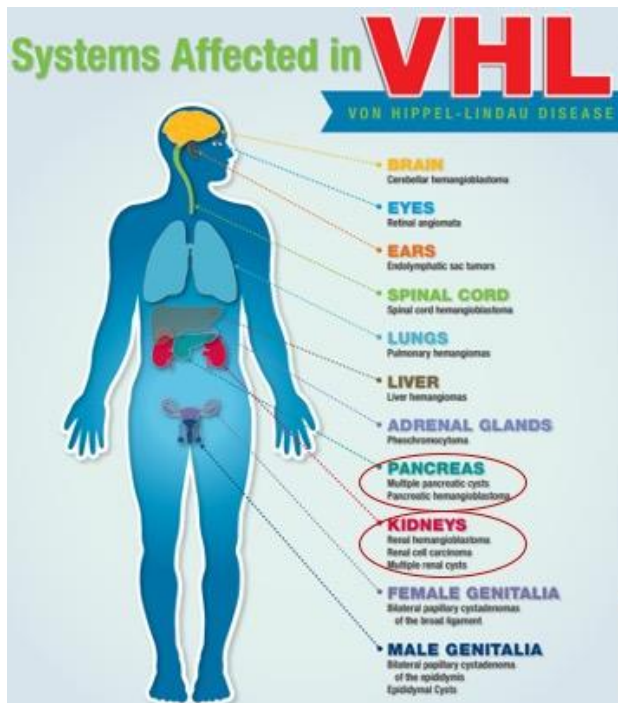


Hemangioblastoma:

- Growths made of newly formed blood vessels
- Typically noncancerous
- Can cause symptoms:
 - Headaches
 - Vomiting
 - Weakness of the arms and legs
 - Problems with balance
 - Vision loss
- Frequently seen in young adulthood
- Screen for these with MRIs and ophthalmology exam

Maher ER, Neuwirth HP, Richard S. von Hippel-Lindau Disease: a clinical and scientific review. *Eur J Hum Genet*. 2021;29:617–28.
 van Leeuwenhorst RS, Alkhalaf S, Linka JP, et al. von Hippel-Lindau Syndrome. 2020 May 17 [updated 2023 Sep 6]. In: Adam MP, Ardinger HH, Fishman WA, et al., editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2023. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8911111/>
 VHL Alliance (2021). What You Need to Know About VHL. Boston, MA: VHL Alliance

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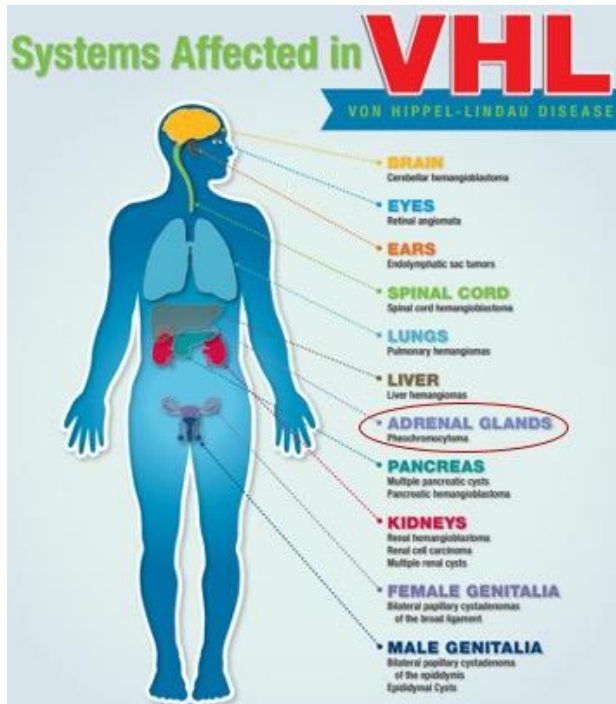


Cancer:

- People with VHL are at an increased risk for developing types of kidney cancer and pancreatic cancer
 - Clear Cell Renal Cell Carcinoma
 - Pancreatic Neuroendocrine Tumor
- Goal of screening is to identify these lesions when they are small and have not yet spread to other areas of the body
- Treatment usually involves surgery

Maher ER, Neuwirth HP, Richard S. von Hippel-Lindau Disease: a clinical and scientific review. *Eur J Hum Genet*. 2021;29:617–28.
 van Leeuwenhorst RS, Alkhalaf S, Linka JP, et al. von Hippel-Lindau Syndrome. 2020 May 17 [updated 2023 Sep 6]. In: Adam MP, Ardinger HH, Fishman WA, et al., editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2023. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8911111/>
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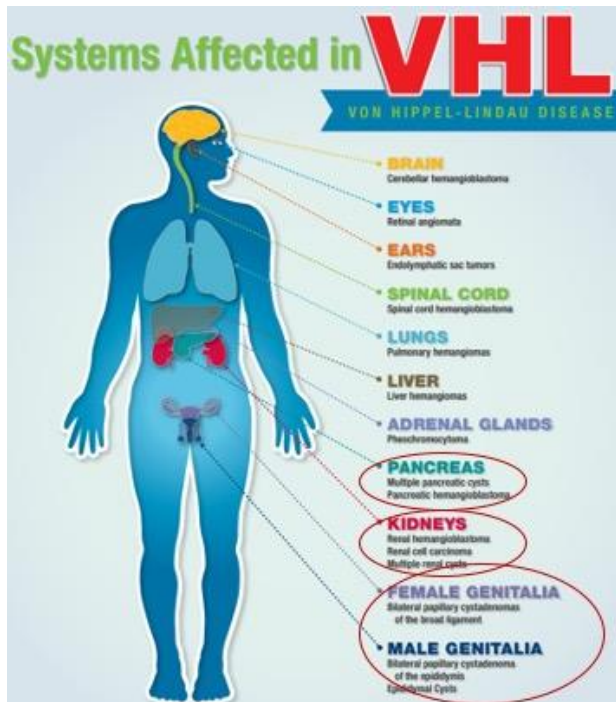
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Pheochromocytoma:

- Tumor found on the adrenal glands (hormone-producing glands that sit on top of the kidneys)
- Typically noncancerous
- May cause symptoms:
 - Headaches
 - Panic attacks
 - Excess sweating
 - High blood pressure (resistant to medication)
- Screen for these through imaging and bloodwork

Maher ER, Neumann HP, Richard S. von Hippel-Lindau disease: a clinical and scientific review. *Sur J Hum Genet*. 2001;69(2):20-28.
van Lennetwilde AS, Ahnadi S, Linka TP, et al. Von Hippel-Lindau syndrome. 2000 May 27 [Updated 2008 Sep 6]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *Genetics Home Reference* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from:
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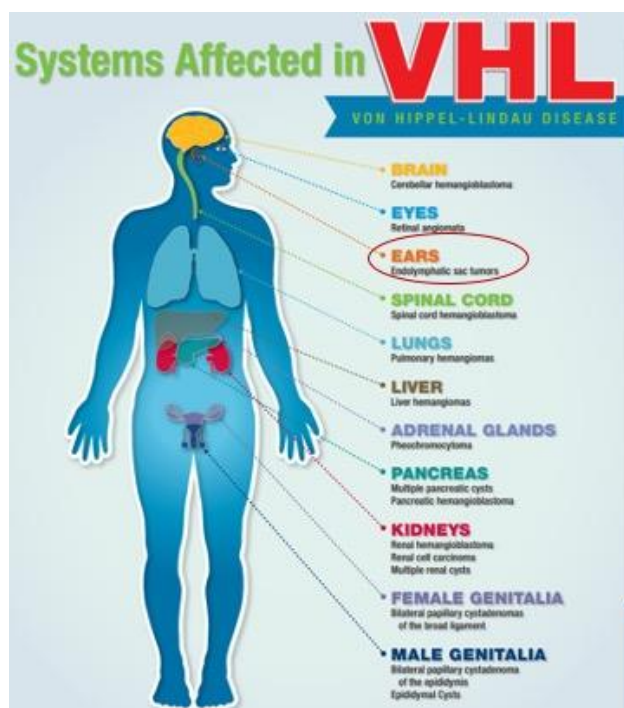


Cysts:

- Sac-like pocket of tissue that contains fluid, air or other substances
- Can develop in the kidneys, pancreas and genital tract
- Frequently cause no symptoms but should be monitored for changes
- Screen for these through imaging

Maher ER, Neumann HP, Richard S. von Hippel-Lindau disease: a clinical and scientific review. *Sur J Hum Genet*. 2001;69(2):20-28.
van Lennetwilde AS, Ahnadi S, Linka TP, et al. Von Hippel-Lindau syndrome. 2000 May 27 [Updated 2008 Sep 6]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *Genetics Home Reference* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from:
VHL Alliance (2020). What You Need to Know About VHL. Boston, MA: VHL Alliance





Endolymphatic Sac Tumor

- Noncancerous tumors in the inner ear
- Can cause complications:
 - Hearing loss in one or both ears
 - Ringing in the ears
 - Problems with balance
- Only seen in ~10% of people with VHL
- Screen for these with MRIs

Maher RA, Neumann HP, Richard S. von Hippel-Lindau Disease: a clinical and scientific review. *Eur J Hum Genet*. 2011;19:613-21.
 von Hippel-Lindau AL, Almog S, Lindh P, et al. von Hippel-Lindau Syndrome. 2000 May 15 [updated 2018 Sep 4]. In: Adams MP, Aschinger HE, Pappas BA, et al., editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2008. Available from: VHL Alliance (2015). What You Need to Know About VHL. Boston, MA: VHL Alliance.

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When Do Symptoms Occur?

	Ages at Diagnosis	Most common age diagnosed	Frequency in patients
Central Nervous System			
Retinal hemangioblastomas	0-68 yrs	12-25 yrs	23-60%
Endolymphatic sac tumors	12-46 yrs	24-35 yrs	10-25%
Cerebellar hemangioblastomas	9-78 yrs	18-25 yrs	44-72%
Brain stem hemangioblastomas	12-36 yrs	24-35 yrs	10-25%
Spinal cord hemangioblastomas	12-66 yrs	24-35 yrs	13-50%
Viscera			
Renal cell carcinoma or cysts	16-67 yrs	25-50 yrs	25-60%
Pheochromocytomas*	4-58 yrs	12-25 yrs	10-20%**
Pancreatic tumor or cyst	5-70 yrs	24-35 yrs	35-70%
Epididymal cystadenomas	17-43 yrs	14-40 yrs	25-60% of males
APMO or broad ligament cystadenomas	16-64 yrs	16-46 yrs	est. 10% of females
* Includes the 20% of these tumors that occur outside the adrenal gland, also called paragangliomas.			
** Frequency of pheochromocytoma varies widely depending on genotype. Refer to Table 2.			

Table 1. Occurrence and age of onset in VHL: Compiled from a survey of papers from 1976 through 2004, and including data from the VHL Alliance.
 VHL Alliance (2015). What You Need to Know About VHL. Boston, MA: VHL Alliance

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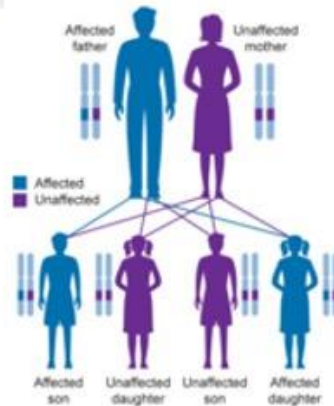
How Common is VHL?

- 1 in 36,000 have VHL
 - 10,000 people with VHL in the U.S.
 - 200,000 people worldwide
- Occurs equally in men and women
- Has been reported in all ethnic groups

van Leeuwen RS, Ahmad S, Links TP, et al. Von Hippel-Lindau Syndrome. 2000 May 17 [Updated 2018 Sep 6]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from:

How is VHL Inherited?

- *VHL* gene
- Each person receives one copy of every gene from each of their parent
- If one parent has a mutation there is a 50/50 chance of it being passed down to each child
- ~20% of the time, someone is the first in their family to have VHL
 - Their parents do not have it
 - They could pass it down to their children



van Leeuwen RS, Ahmad S, Links TP, et al. Von Hippel-Lindau Syndrome. 2000 May 17 [Updated 2018 Sep 6]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from:

Does My Specific Mutation Matter?

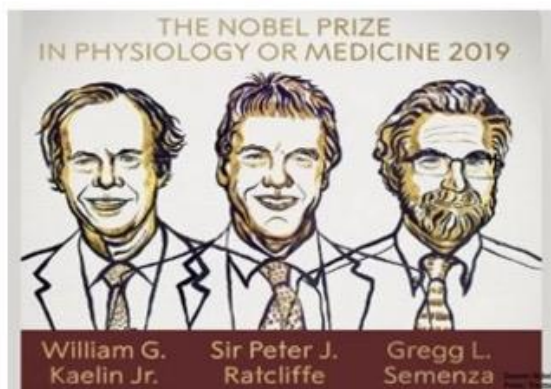
Yes!

- Genotype-Phenotype correlations exist
 - Type 1 = lower risk for pheo
 - Type 2 = higher risk for pheo
- Important to have DNA analysis

VHL Subtype	VHL Mutation Type	High Risk Manifestations	Low Risk Manifestations
Type 1	Deletions, insertions, truncations, missense	Central Nervous System hemangioblastomas Retinal hemangioblastomas Renal cell carcinoma	Pheochromocytoma
Type 1B	Contiguous gene deletions encompassing VHL	Central Nervous System hemangioblastomas Retinal hemangioblastomas	Pheochromocytoma, Renal Cell Carcinoma (risk may increase if C3 or f10 remains increased)
Type 2A	Missense; e.g. p.Y98H, p.Y112H, p.V116F	Central Nervous System hemangioblastomas Retinal hemangioblastomas Pheochromocytoma	Renal Cell Carcinoma
Type 2B	Missense; e.g. p.R167Q, p.R167W	Central Nervous System hemangioblastomas, Retinal hemangioblastomas Renal cell carcinoma	
Type 2C	Missense; e.g. p.V84L, p.L188V	Pheochromocytoma only	

Hes F, Zewald R, Peeters T, et al. Genotype-phenotype correlations in families with deletions in the von Hippel-Lindau (VHL) gene. Hum Genet. 2000;106(4):425-431.;
 Maher ER, Webster AR, Richards FM, et al. Phenotypic expression in von Hippel-Lindau disease: correlations with germline VHL gene mutations. Journal of medical genetics. 1996;33(4):328-332.;
 Chen F, Slike L, Kishida T, Muirhead J, Tisherman SE, Zbar B. Genotype-phenotype correlation in von Hippel-Lindau disease: identification of a mutation associated with VHL type 2A. Journal of medical genetics. 1996;33(8):716-717.

Exciting News in VHL



Iliopoulos O, Ohh M, Kaelin WG, Jr. 1998. pVHL19 is a biologically active product of the von Hippel-Lindau gene arising from internal translation initiation. Proceedings of the National Academy of Sciences of the United States of America 95(20):11661-11666.

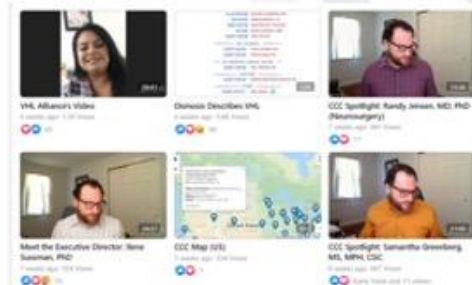
VHL Alliance Clinical Care Centers

- VHLA designated
- Provide required surgical, screening, and specialty services
- Allow patients to have a 'one stop shop' for comprehensive care



VHLclinic@hci.utah.edu

What You Need to Know About VHL



I have VHL

I may have a pheochromocytoma. If I need surgery, I may need **α and β blockers.**

OR

I may have post-operative adrenal insufficiency.

VHL ALLIANCE

For more info, visit VHL.org

Possible VHL Lesions, S/Sx

- Brain / Spinal Hemangioblastoma**
Headaches, dizziness, vomiting, back pain, numbness, tingling
- Retinal Hemangioblastoma**
Blurred vision, floaters, scotomata
- Endolymphatic Sac Tumor**
Tinnitus, hearing loss, vertigo
- Pheochromocytoma / Tumor / Cancer**
Intermittent flush (sweating of face, blushing), headache, blood pressure of above normal, irregular irregularity, malaise, anxiety, diarrhea
- Pheochromocytoma, Paraganglioma**
High blood pressure, heart palpitations, fast heart rate, excessive sweating, flushing, anxiety
- Kidney Cysts, Renal Cell Carcinoma**
None, back pain, hematuria, fatigue
- Cystadenomas (for both M and F)**
pain, constipation, bloating, nausea, vomiting, weight loss, ovarian cancer

Long and full map: VHL.org

2020 Annual VHL Family Meeting
October 24, 2020

Living with VHL:
Coping with the
Diagnosis and Medical
Management

Yelena Wu, PhD

Living with VHL: Taking care of one's psychological health

Yelena P. Wu, PhD



Overview

- Learning about the VHL diagnosis – reactions in the short and long term
- Coping with VHL screening and VHL-associated health concerns
- Addressing common challenges to managing VHL screenings and care



Learning about the VHL diagnosis: Things that can affect one's reactions

- Circumstances around how someone learns they had VHL
 - Family member diagnosed with VHL and cascade testing
 - Personal history of health problems that led to testing for VHL
 - Testing for another medical issue that resulted in learning about VHL
- Personal experience with VHL-associated health problems in oneself or with family
 - Long diagnostic odyssey? Treated effectively? Traumatic?
- Prior experiences with health conditions and medical system



Learning about the VHL diagnosis: Things that can affect one's reactions

- Other events or features of life when learning about the diagnosis
 - Biggest priorities or tasks at the time: Work, school, family, social life, romantic partners, hobbies, other passions
- Financial impact (Costs, health insurance)
- Distance to medical care needed for follow-up
- Social support
 - Processing the diagnosis
 - Support on ongoing screening or health issues



Learning about the VHL diagnosis: Possible short-term reactions

- Surprise or shock
 - “This makes sense” or gives a name to it
 - Helps to explain personal or family health history
 - Desire to avoid
 - Guilt
 - Anger
- These reactions can lead individuals to:
- Seek out more information
 - Talk with others, receive social support
 - Make steps towards screening or follow-up appointments
 - Let the news “sink in” and take a pause



Living with the VHL diagnosis: Possible longer-term reactions

- Burnout from screening, etc.
 - Periods of apathy and “not caring”
 - Other periods of caring more (e.g., family member steps in to support, renewed motivation because of children)
 - This is “just part of my life” or who I am
- These reactions can lead individuals to:
- Not schedule screening or medical appointments at all
 - Inconsistent screening
 - Regular screening



Coping with VHL: Things that may help

- Lessons learned from our patients and the psychological literature
- Cognitive or thinking strategies
 - Viewing VHL-related screenings as another part of regular preventive care
 - Thinking of the screenings as a proactive way to take control of your health and ensure that you will continue to be able to ____ (fill in the blank with what you enjoy or what is important to you)
 - Thinking about how VHL fits with the rest of who you are
 - Mindfulness strategies



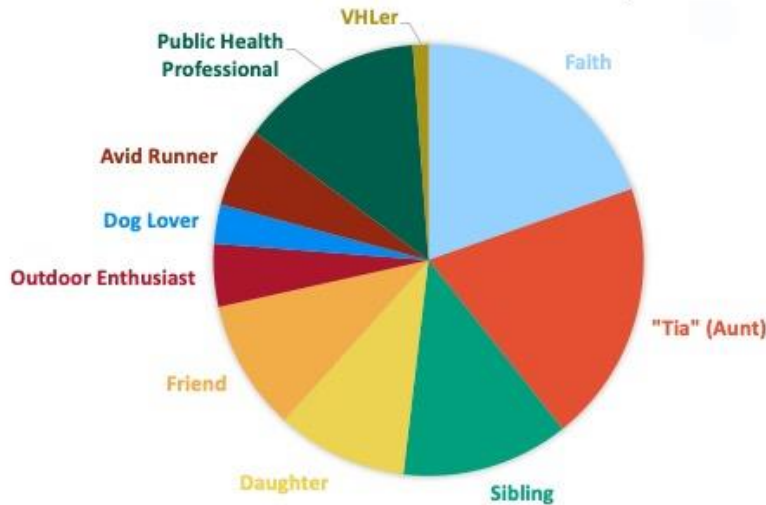
Mindfulness strategies

- Paying attention, on purpose, in the present moment, without judgment
 - Observation of thoughts, sounds, bodily sensations
 - Strive for 10 minutes a day
- Websites:
 - <https://counselingcenter.utah.edu/services/audiomindfulness.php>
- Books:
 - Full catastrophe living...By Jon Kabat-Zinn
- App's:
 - Calm, Headspace, Buddhify

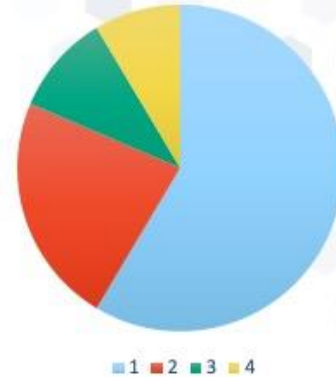


Coping with VHL: Things that may help

- How does VHL fit with the rest of you



My Identity



Coping with VHL: Things that may help

- Knowing the signs (different for everyone) when it is challenging
 - E.g., Mood changes, not caring, stress related to VHL, people around you alerting to a change
- Seeking support
 - Family, friends, others in your life
 - Medical team, including social work or other behavioral providers
 - VHL Alliance
 - Behavioral health provider



Common challenges to managing VHL screenings and care: Scanxiety in adults

- Recognize that some level of worry or anxiety about scans is normal
- Know when this usually arises for you (1 month before? The day before?) and what your worry signs are (poor sleep? Jitters? Bad mood?)
- What has gone well or not in the past
- Come up with strategies for coping with the worry that are a good fit for you
 - Mindfulness strategies
 - Replacement thoughts
 - Enjoyed activities
 - Talk with someone



- Practice relaxation strategies (with an MRI soundtrack in the background!)



Common challenges: Other family members

- Family members who have VHL
 - Different approaches to and prioritization about screening
 - Unique personal health histories related to VHL (e.g., tumor history)
 - Affects attitudes towards screening
- Family members who do not have VHL
 - Feeling like they don't understand
 - Getting support from these family members



Closing thoughts

- VHL is part of your or your family's life
 - It is one part
- Monitor how you're coping with VHL (and the rest of life)
 - Know the signs for when things are getting challenging for you
 - Ask for feedback from others on this; seek support
- Find self-care strategies that work for you and make a plan for how and when you'll use them



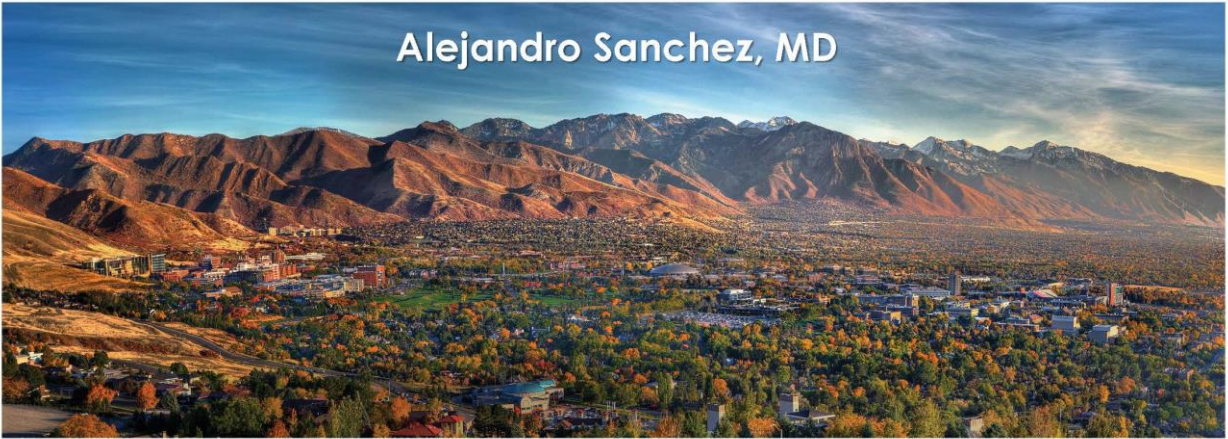
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Urological Findings in VHL

Alejandro Sanchez, MD

Genitourinary Manifestations of Von Hippel-Lindau Disease

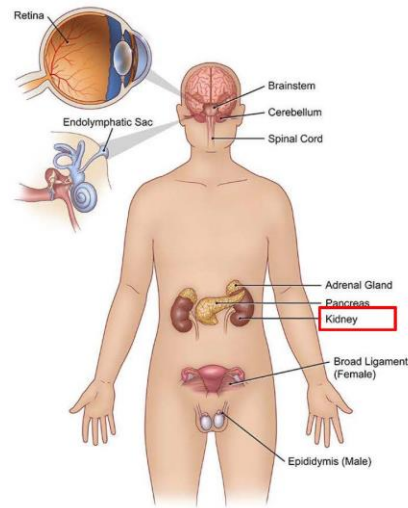
Alejandro Sanchez, MD



Talk Overview

- Renal masses
 - Epidemiology
 - Surveillance
 - Treatment
- Pheochromocytoma/paraganglioma
 - Epidemiology
 - Surveillance
 - Treatment
- Epididymal / broad ligament cystadenomas

What genitourinary organs are affected by VHL?



Visual Art: © 2013 The University of Texas MD Anderson Cancer Center

Epidemiology of sporadic renal cancer vs VHL

Sporadic RCC

Estimated New Cases						
			Males	Females		
Prostate	191,930	21%			Breast	276,480 30%
Lung & bronchus	116,300	13%			Lung & bronchus	112,520 12%
Colon & rectum	78,300	9%			Colon & rectum	69,650 8%
Urinary bladder	62,100	7%			Uterine corpus	65,620 7%
Melanoma of the skin	60,190	7%			Thyroid	40,170 4%
Kidney & renal pelvis	45,520	5%			Melanoma of the skin	40,160 4%
Non-Hodgkin lymphoma	42,380	5%			Non-Hodgkin lymphoma	34,860 4%
Oral cavity & pharynx	38,380	4%			Kidney & renal pelvis	28,230 3%
Leukemia	35,470	4%			Pancreas	27,200 3%
Pancreas	30,400	3%			Leukemia	25,060 3%
All Sites	893,660	100%			All Sites	912,930 100%

VHL

- Autosomal Dominant
- 1 in 36,000

Siegel RL, et al. *CA Cancer J Clin*, 2020

Epidemiology of sporadic renal cancer vs VHL

	Sporadic RCC	VHL
Demographics		
Age at presentation	60-70 yr	40-45 yr
Sex (M:F)	2:1	1:1
Race/ethnicity	Lowest among Asian Americans and Pacific Islanders	
Risk factors	Obesity, diabetes, hypertension, smoking	Autosomal dominant inheritance
Masses at presentation	Unilateral, unifocal	Bilateral, multifocal

Ball MW, et al. *J Clin Oncol*, 2020

What is the incidence of VHL in de novo advanced ccRCC?

JAMA Oncology | Original Investigation

Prevalence of Germline Mutations in Cancer Susceptibility Genes in Patients With Advanced Renal Cell Carcinoma

Maria I. Carlo, MD; Semanti Mukherjee, PhD; Diana Mandelker, MD, PhD; Joseph Vijai, PhD; Yelena Kemel, MS, ScM; Liying Zhang, MD, PhD; Andrea Knezevic, MS; Sujata Patil, PhD; Ozge Ceyhan-Birsoy, PhD; Kuo-Cheng Huang, MD; Almedina Redzematovic, MS; Devyn T. Coskey, BS; Carolyn Stewart, BA; Nisha Pradhan, BA; Angela G. Arnold, MS; A. Ari Hakimi, MD; Ying-Bel Chen, MD, PhD; Jonathan A. Coleman, MD; David M. Hyman, MD; Marc Ladanyi, MD; Karen A. Cadoo, MD; Michael F. Walsh, MD; Zsolt K. Stadler, MD; Chung-Han Lee, MD, PhD; Darren R. Feldman, MD; Martin H. Voss, MD; Mark Robson, MD; Robert J. Motzer, MD; Kenneth Offit, MD, MPH

- N=254 patients germline tested
- Median age 56 (range 13-79)
- 211 (83.1%) Male
- 177 (69.7%) with ccRCC
- 1 patient with *VHL* mutation

Carlo M, et al. *JAMA Oncology*, 2018

What is the risk of RCC among VHL patients?

Clinical manifestations of von Hippel-Lindau disease

	Ages at diagnosis	Most common ages at dx	Frequency in patients CNS
Viscera			
Renal cell carcinoma or cysts	16-67 yrs	25-50 yrs	25-60 percent
Pheochromocytomas*	4-58 yrs	12-25 yrs	10-20 percent†
Pancreatic tumor or cyst	5-70 yrs	24-35 yrs	35-70 percent
Epididymal cystadenomas	17-43 yrs	14-40 yrs	25-60 percent of males*
Adnexal papillary cystadenoma of mesonephric origin (broad ligament cystadenoma)	16-64 yrs	16-46 yrs	Estimated 10 percent of females

* Includes the 20 percent of lesions that occur outside the adrenal gland, also called paragangliomas.

† Frequency of pheochromocytoma varies widely depending on genotype.

Courtesy of Eric Jonasch, MD.

Maher ER, et al. *Q J Med*, 1990
 Chahoud J, et al. *W Journal of Urology*, 2020
 Linehan, *Genome Research*, 2012

RCC risk among VHL patients differs by mutation type

- VHL type is broken down by risk of pheochromocytoma:
 - Type 1: LOW risk of pheochromocytoma
 - Type 2: HIGH risk of pheochromocytoma

	VHL type	Pheochromocytoma	RCC	Hemangioblastomas
*	1A	Low	High	High
	1B	Low	Low	High
	2A	High	Low	High
*	2B	High	High	High
	2C	High	No	No

*Highest risk of RCC

Details of screening for RCC

- Imaging:
 - Start at age 15 yr
 - Imaging every 2 years if **no** tumor found
 - MRI should be done consecutively with neuroaxis protocol
 - Can alternate with renal ultrasound if no concerning lesions and MRI concerns
 - If contraindications present: MRI (+/- contrast) > MRI (w/o contrast) > CT (w/ contrast) > CT (w/o contrast) > ultrasound (kidneys, adrenals, and pancreas only)
- Physical exam/labs:
 - Adenopathy, varicocele, stigmata of chronic kidney disease or paraneoplastic syndromes
 - Renal function, liver function, LDH, calcium, neutrophil-to-lymphocyte ratio

Chahoud J, et al. *W Journal of Urology*, 2020

How does surveillance change by mass size?

- Masses < 3 cm -> assess growth kinetics with MRI every 3-6 months for one year
- If ≥ 3 cm recommend nephron-sparing technique at academic center with VHL expertise
 - Thermal ablative techniques (RFA/Cryo), should be used in patients with small tumors and high-operative risk
- What about pregnancy/family planning?
 - Surveillance should be performed before planning conception if possible
 - MRI without contrast can be done during pregnancy
 - AS for renal masses < 4 cm is preferred during pregnancy and treatment delayed until after delivery

Chahoud J, et al. *W Journal of Urology*, 2020

What are the growth characteristics of renal masses in VHL?

- If growing 2-4 mm (expected) per year -> repeat imaging every 6 months for first year and every year for subsequent two years
- If growing > or equal to 5 mm per year -> imaging every 3-6 months until treated or stable growth rate
- If stable renal mass for 3 years, consider imaging every 2 years

Chahoud J, et al. *W Journal of Urology*, 2020

What are the growth characteristics of renal masses in VHL?

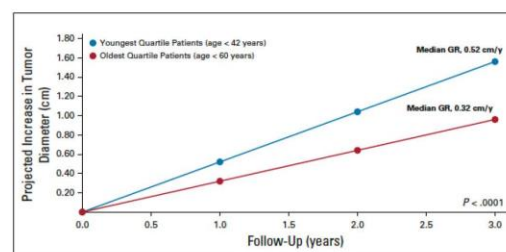
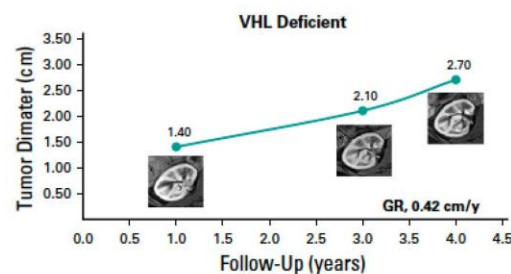


FIG 4. VHL-deficient tumor growth by age. GR, growth rate.

Ball MW, et al. *J Clin Oncol*, 2020

What is the role of renal mass biopsy in VHL?

- Rarely indicated
- Avoid for cystic lesions
- Specific situations:
 - Prior thermal ablation or suspected recurrence
 - Atypical radiographic appearance suggestive of alternate diagnosis to primary renal malignancy (e.g., inflammation)
 - Concurrent or prior extra-renal malignancy that could confound diagnosis



Chahoud J, et al. *W Journal of Urology*, 2020

VHL ccRCC treatment: "3 cm rule"

TABLE 2. Comparison of tumor size and metastases

No. Metastases/No. Pts. (%)	Tumor Size (cm.)
0/52	3.0 or Less
1/17 (6)	3.2–4.0
2/10 (20)	4.1–5.5
4/12 (33)	6.0–10.0
4/5 (80)	10.0 or Greater

Walther MM, et al. *J Urol*, 1999

What are the goals of ccRCC treatment in VHL?

- “Reset the clock”
- Minimize the risk of metastases
- Minimize the risk of chronic kidney disease through nephron-sparing techniques



Bindrup MLM, et al. *Journal of Medical Genetics*, 2017
Walther MM, et al. *J Urol*, 1999

VHL ccRCC treatment: surgical approach

Open

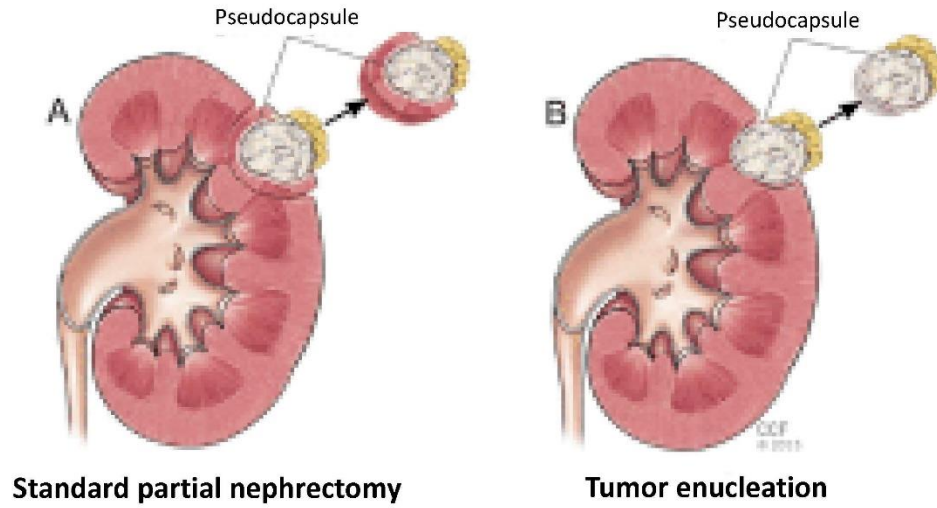


Robotic



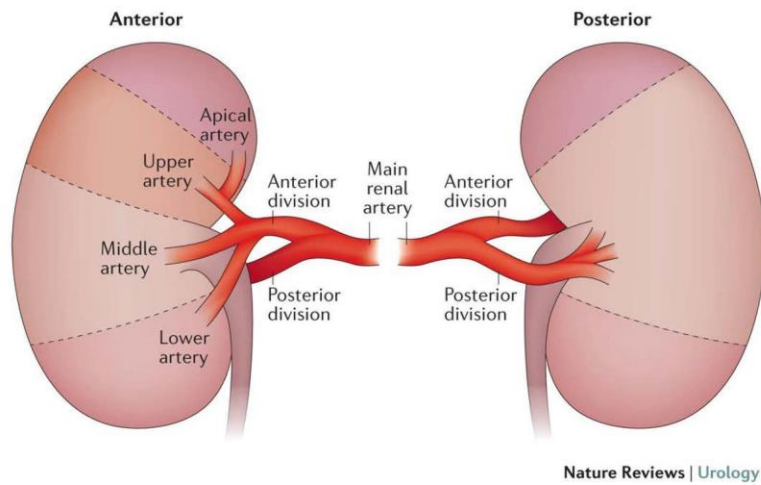
Russo P and Mano R, *Korean J Urol*, 2014

VHL ccRCC treatment: enucleation vs wide resection



Blackwell RH, et al. *Urology*, 2017

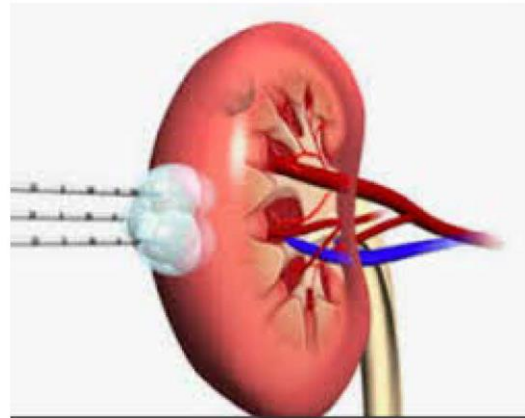
VHL ccRCC treatment: selective clamping or off-clamp partial nephrectomy



Alenezi A, et al. *Nat Reviews Urol*, 2016

VHL ccRCC treatment: ablation

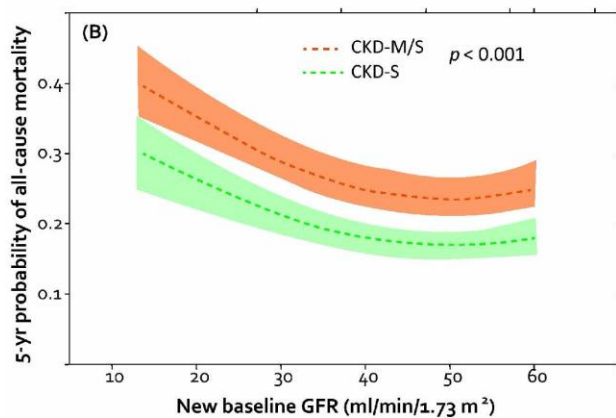
- Limited VHL-specific data
- Extrapolating from sporadic ccRCC data (usually solitary lesions)
 - Size
 - Location
 - Risk of local recurrence higher
- Case selection is key
- May complicate subsequent surgeries and possibly affect tumor progression



Shuch B and Linehan, *Nat Reviews Urol*, 2012

VHL ccRCC treatment: renal dysfunction

- Chronic kidney disease (CKD) is a risk factor for cardiovascular morbidity
- Surgical CKD differs from medical CKD



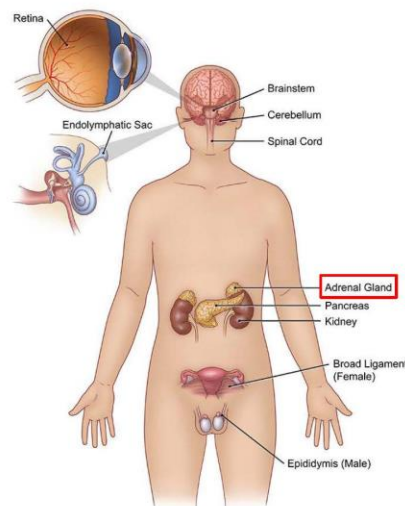
Lane B, et al. *Eur Urol*, 2015

Important patient counseling regarding management of renal masses

- Urologist should lead the counseling process (+/- nephrology), consider all management strategies, and review the most common and serious urologic and non-urologic morbidities of each treatment pathway
- Provide perspectives on tumor biology, risk assessment including tumor size and imaging characteristics
- Renal function recovery related to diagnosis and management of renal masses
- Referral to nephrology for management of CKD if high risk or GFR is < 45 in patient with pre-existing CKD, or those in whom eGFR < 30 after intervention

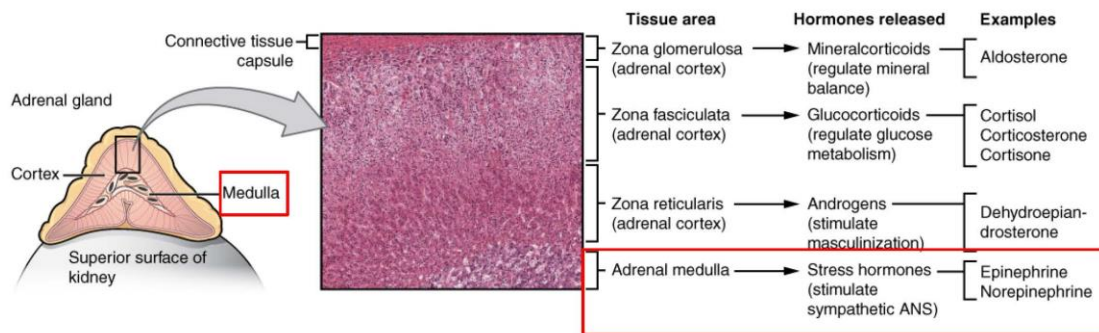
Chahoud J, et al. *W Journal of Urology*, 2020

What are the genitourinary organs affected by VHL?



Visual Art: © 2013 The University of Texas MD Anderson Cancer Center

What is the pheochromocytoma and paraganglioma?



- Up to 20% can be extra-adrenal (skull base to bladder), aka paragangliomas

Pheochromocytomas present in VHL type 2

VHL type	Pheochromocytoma	RCC	Hemangioblastomas
2A	High	Low	High
2B	High	High	High
2C	High	No	No

Clinical manifestations of von Hippel-Lindau disease

	Ages at diagnosis	Most common ages at dx	Frequency in patients CNS
Viscera			
Renal cell carcinoma or cysts	16-67 yrs	25-50 yrs	25-60 percent
Pheochromocytomas*	4-58 yrs	12-25 yrs	10-20 percent†
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* Includes the 20 percent of lesions that occur outside the adrenal gland, also called paragangliomas.

† Frequency of pheochromocytoma varies widely depending on genotype.

Courtesy of Eric Jonasch, MD.

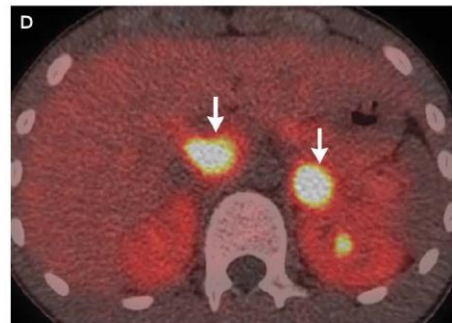
Pheochromocytoma presentation

- About 1/3 will be symptomatic
- VHL-associated vs sporadic:
 - Younger age
 - Often multiple
 - Can be extra-adrenal
 - Less likely to be symptomatic
- Symptoms of catecholamine production: hypertension, diaphoresis, tachycardia, and apparent mood changes

Walther, J Urol, 1999
Baghai M, et al. Arch Surg, 2002

Pheochromocytoma in VHL: screening

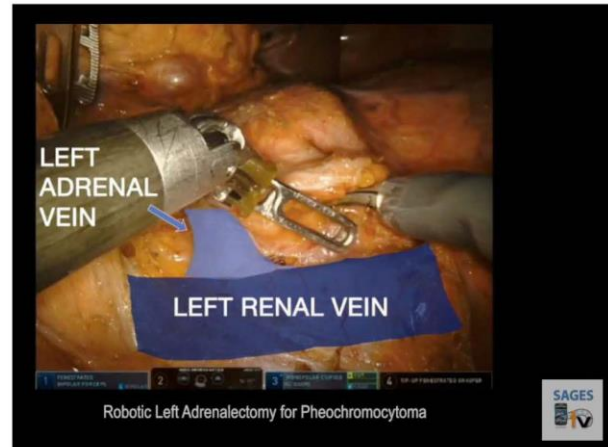
- Radiographic imaging via plasma fractionated metanephrines or 24-hour urine fractionated metanephrines and catecholamines
- Conventional imaging (CT or MRI) is adequate for adrenal lesions
- Conventional imaging is **not** adequate for extra-adrenal lesions, consider:
 - Iobenguane I-123 scan
 - Whole body MRI
 - FDG or 68-Ga Dotatate PET CTs



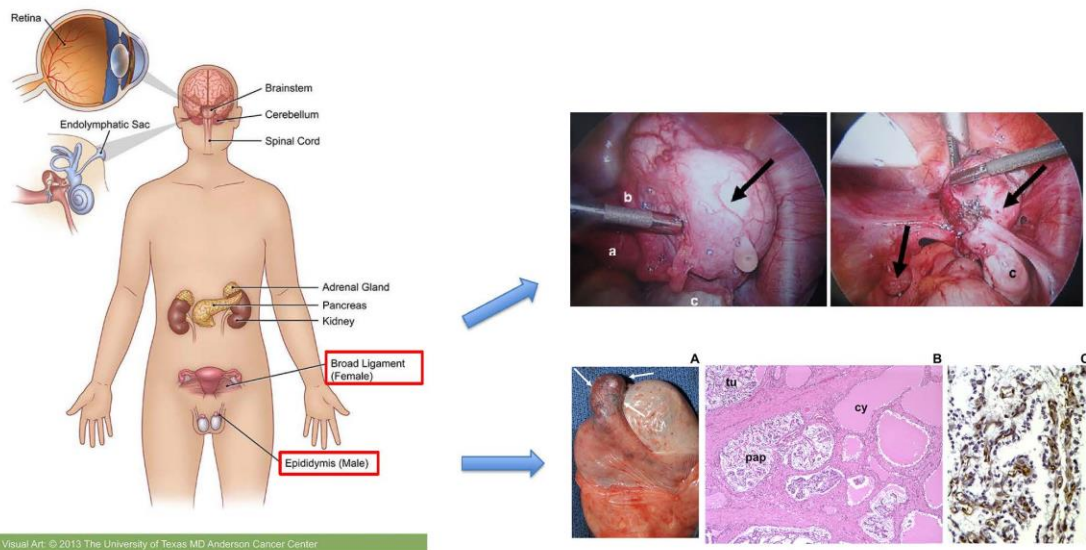
Neumann HPH, et al. NEJM, 2019

Pheochromocytoma in VHL: management

- Symptomatic pheochromocytomas should be surgically removed
- Partial adrenalectomy if possible (minimize the risk of adrenal insufficiency)
- Alpha-adrenergic blockade and other supportive measures needed



What are the genitourinary organs affected by VHL?



Glasker S, et al. *OncoTargets and Therapy*, 2020
Zanotelli D, et al. *Archives of Gynecology and Obstetrics*, 2010

CONCLUSIONS

- Surveillance and early detection is key
- Treatment of genitourinary manifestations in VHL requires a multidisciplinary approach
- Organ-preservation is key in the management of renal and adrenal masses

Thank you

VHL and High-Risk Renal Cancer Clinic Team



2020 Annual VHL Family Meeting
October 24, 2020

VHL and Brain Tumors:
Bench to Bedside

Randy Jensen, MD, PhD



VHL and Brain Tumors: Bench to Bedside

Randy Jensen MD PhD MHPE

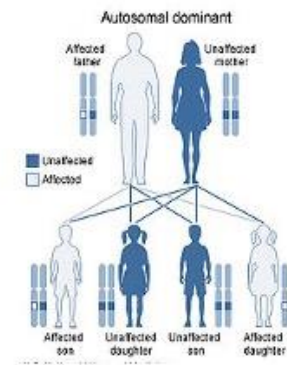
Professor of Neurosurgery, Radiation Oncology, and Oncological Sciences
Vice Chair of Education, Residency Program Director
Huntsman Cancer Institute, University of Utah



von Hippel-Lindau Disease

- Autosomal Dominant, Chr 3p25
 - Retinal angiomas (57%)
 - Cerebellar (55%), medullary (6%), and spinal (14%) hemangioblastomas;
 - Endolymphatic sac tumors
 - Pheochromocytoma (19%)
 - Renal cysts (14%)
 - Renal cell carcinoma (24%)
 - Epididymal cystadenoma (17%)
 - Pancreatic cysts (14%)
 - Pancreatic malignancy (4%)

• Medicine 1989;68:1-29



Von Hippel-Lindau—Brain manifestations

- Dr. Eugen Von Hippel—German ophthalmologist, described **angiomas in the eye** in 1893-1911. His name was originally used only in association with VHL in retina
- Dr. Arvid Lindau, a Swedish pathologist, first described the **angiomas of the cerebellum and spine** in 1926.

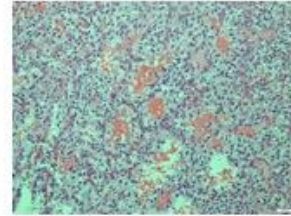


Hemangioblastoma

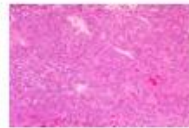
- 1-2.5% of primary intracranial tumors
 - Most common cerebellar tumor of adults
- Young adults to middle age
 - Males slightly predominant
- Cerebellum 75% / Spinal 25%
- 10-20% related to VHL disease
- Maybe associated with polycythemia (secretion of Epo-like factor)



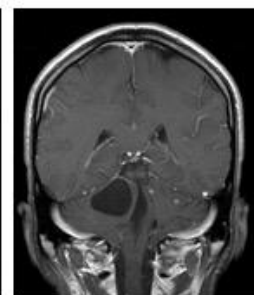
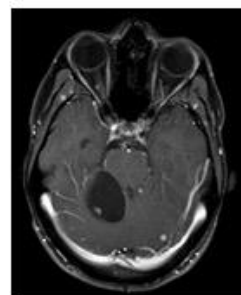
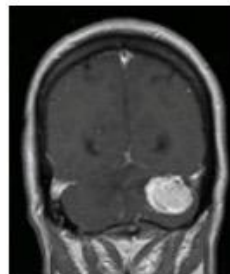
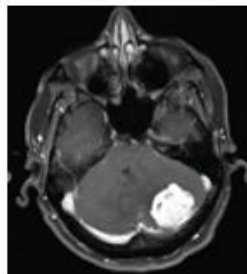
Hemangioblastoma



- WHO grade I tumor
- Stromal cells endothelial cells, pericytes and mast cells
- Undefined cell of origin
- Numerous lipid-containing vacuoles
- “clear cell” morphology—similar to RCC but EMA, panepithelial antigen and cytokeratin negative

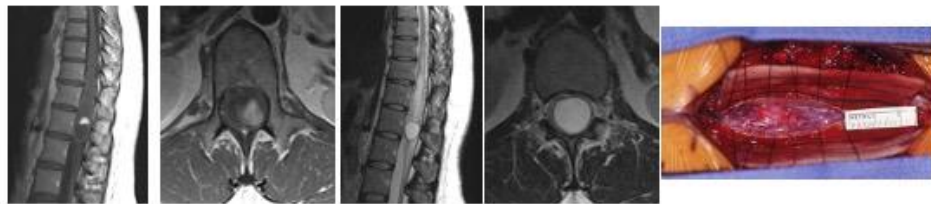


Cerebellar hemangioblastomas



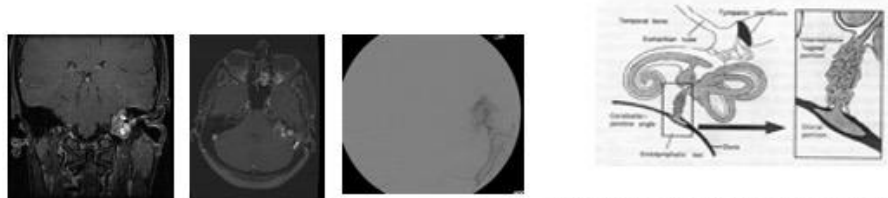
Spinal Hemangioblastoma

- Spinal hemangioblastomas 3-8% of intramedullary tumors
 - Histologically similar to cerebellar lesions
 - Intramedullary
 - Less often cystic, but often syrinx
 - Generally sporadic but 25% have VHL disease
 - Symptomatic at earlier age
 - Multiple tumors



Endolymphatic Sac Tumors

- Not part of the clinical definition
 - recently added to VHL
 - 15% of people with VHL
- Papillary, locally invasive adenocarcinoma described in 1989
 - Hefner, 1989
- Endolymphatic sac—posterior wall of temporal bone
- Hearing loss, balance, and equilibrium



JAMA. 1997; 277:1461-1466; Hum Pathol 2001, 32:1272-1276

Symptoms

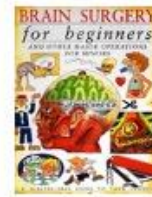
- Cerebellar hemangioblastomas
 - Progressive ataxia
 - Hydrocephalus
- Spinal canal hemangioblastomas
 - Cord compression and root compression



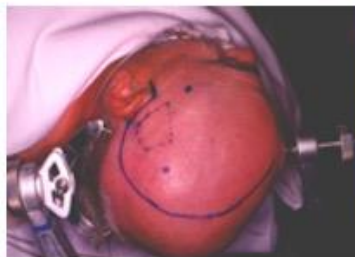
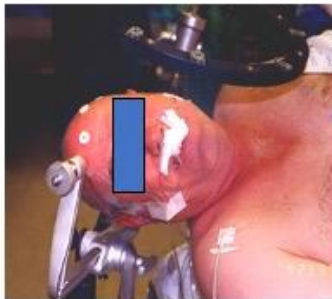
Treatment

Surgery

- Completely remove nodule
- Cyst wall does not need to be removed
- Biopsy not good idea
- Recurrence 15-40%
- No difference between VHL and non-VHL



Frameless navigation



Problem with navigation using only preop MRI



"Nurse, get on the internet, go to SURGERY.COM, scroll down and click on the 'Are you totally lost?' icon."

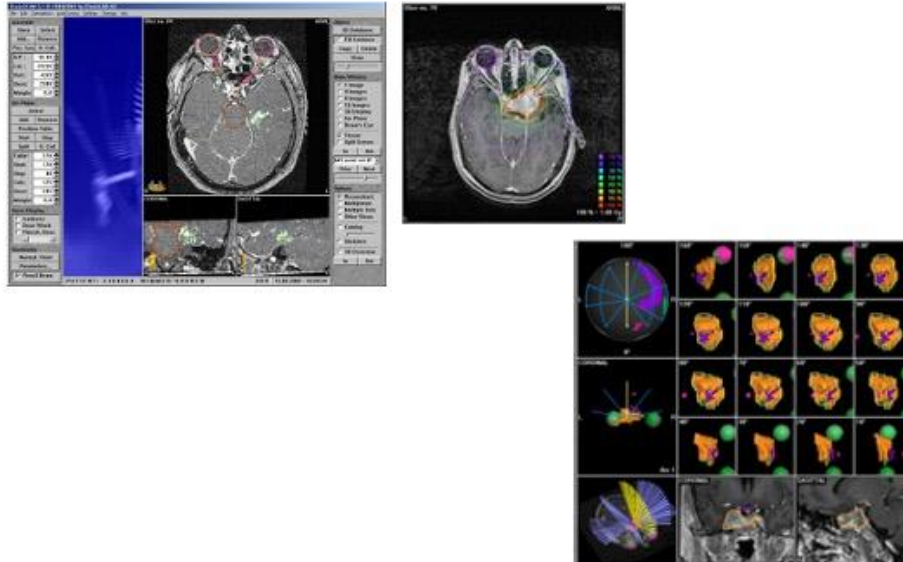


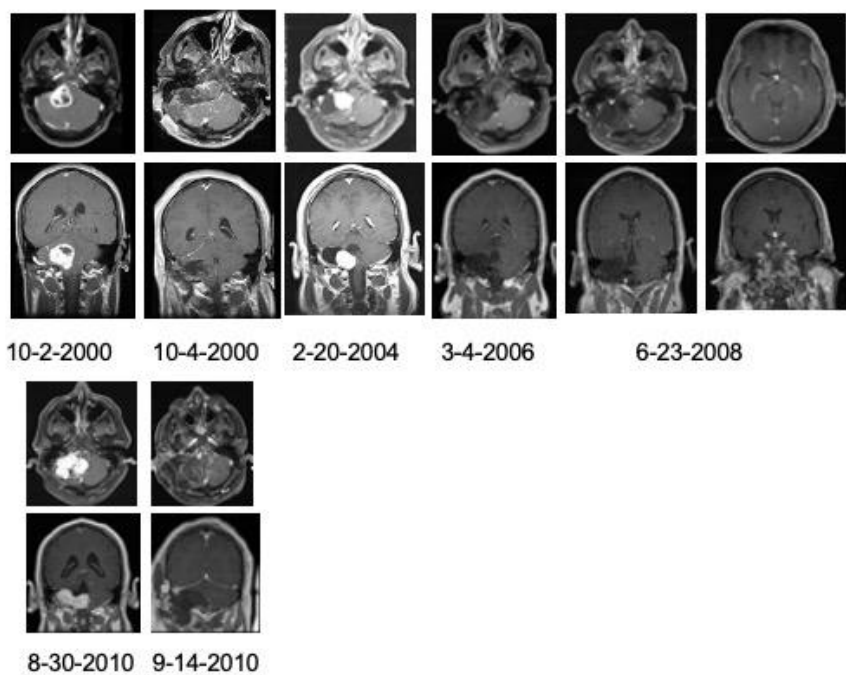
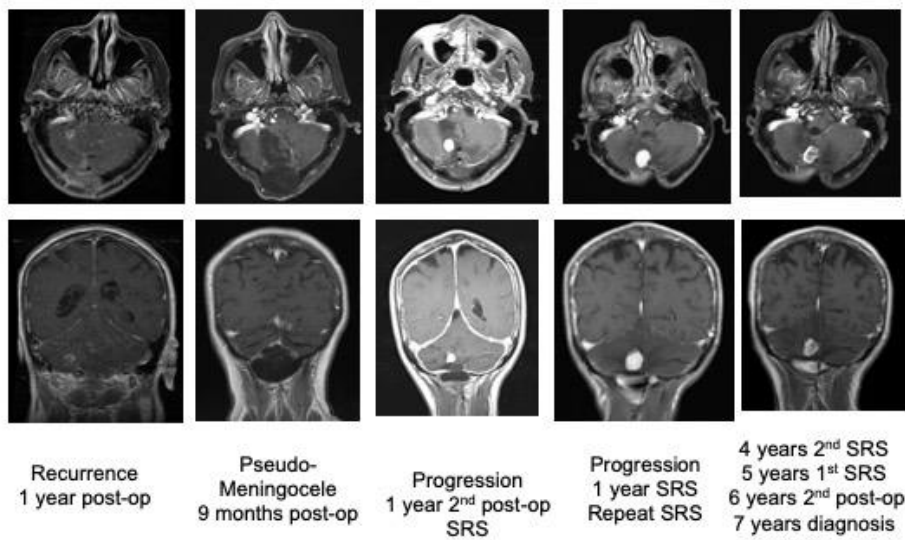
Stereotactic radiosurgery

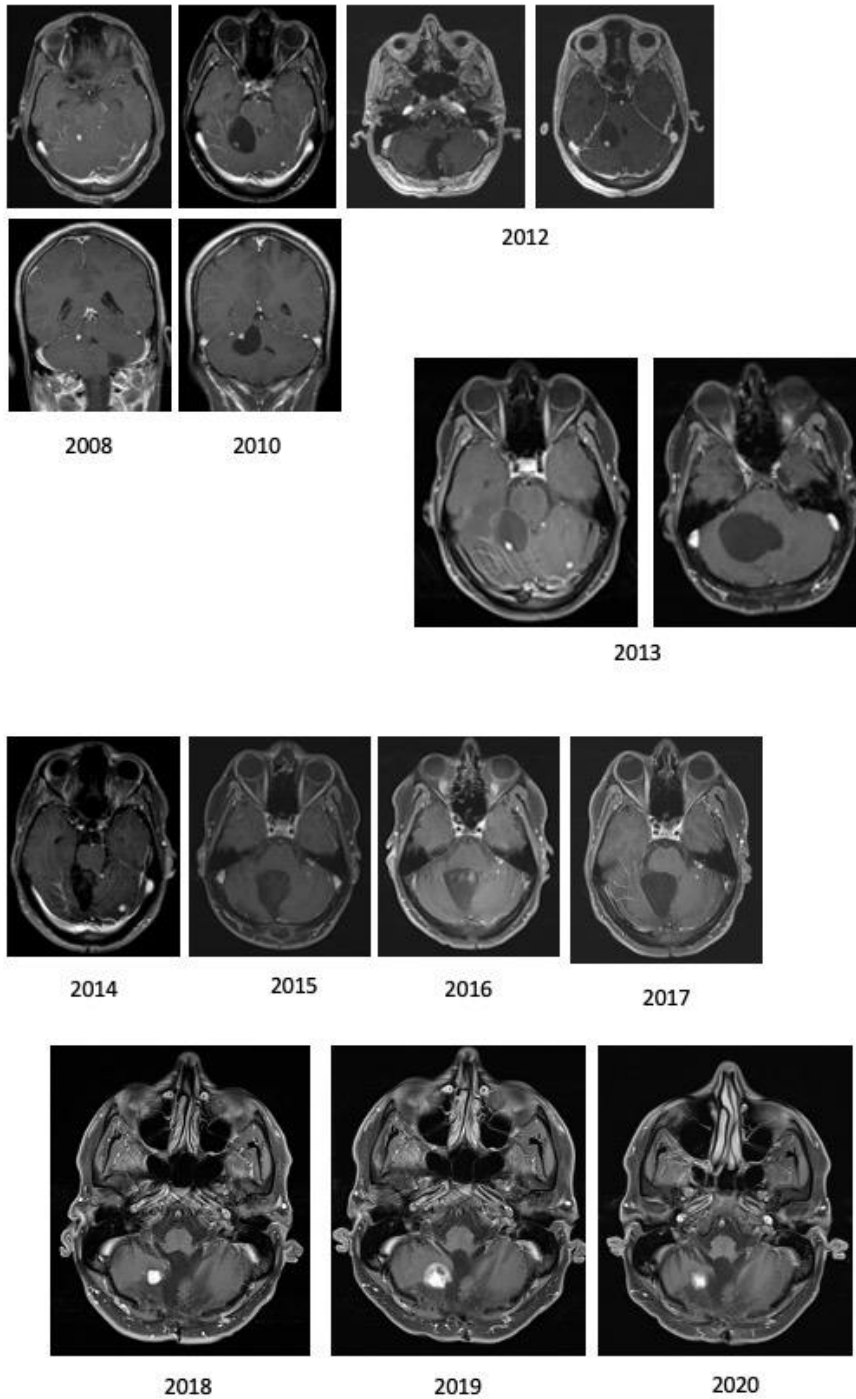
- Lesions less than 2 cm
- Location
- No associated cyst
- May not prevent cyst development
- Asymptomatic

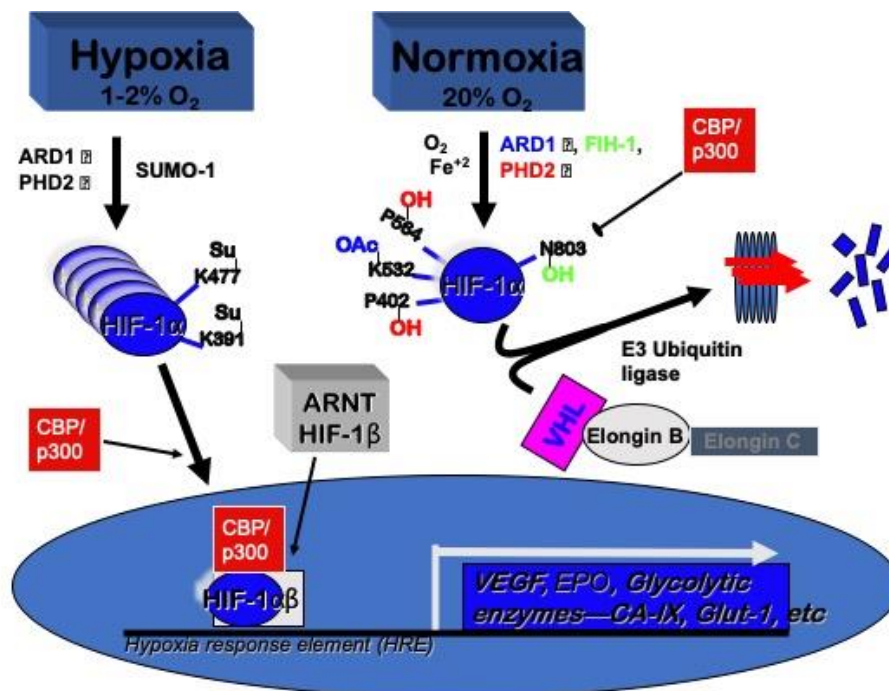


Stereotactic radiosurgery

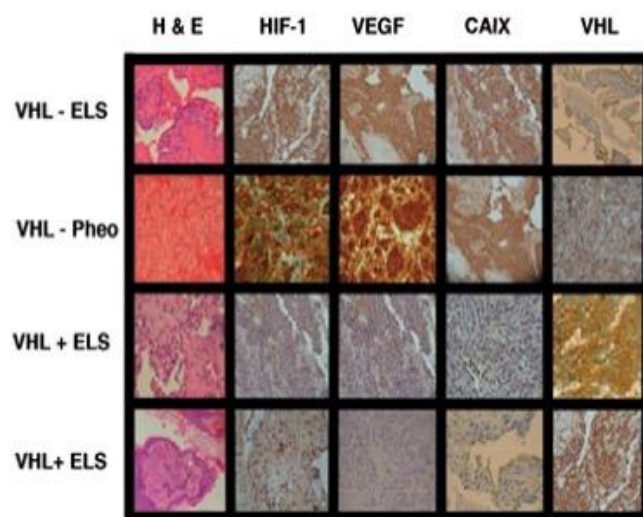


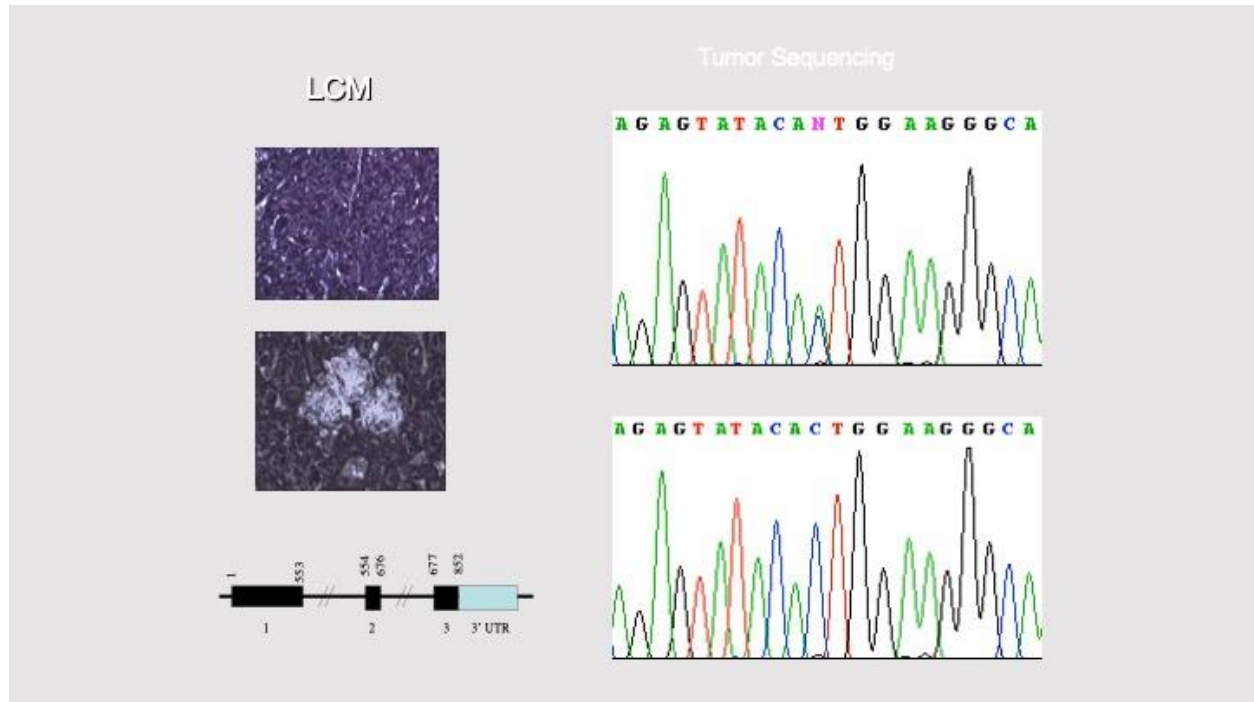






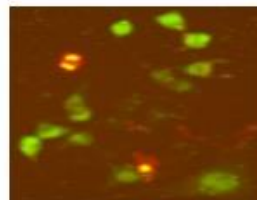
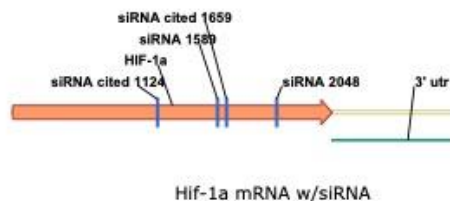
Immunohistochemistry of ELS tumor patients





Patient TP VHL disease

- Heterozygous for G to T mutation at position -1 on Exon 3 splice acceptor sequence in the VHL gene
- This mutation previously reported in patients with VHL, alters the splice acceptor consensus sequence resulting in aberrant splicing of encoded mRNA

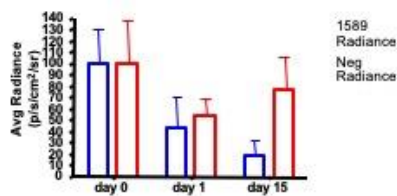
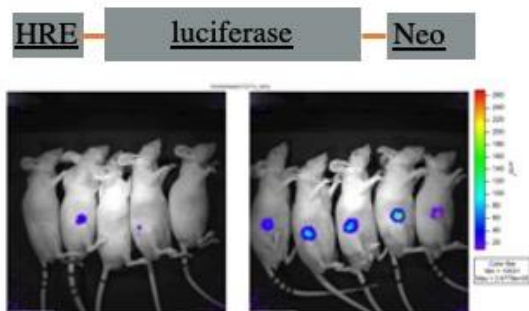


47- CGUCGAAAAGAAAAGUCUCUU
495- GCUUUUUUCUCAGAAUGAAUU
1094- UCUUCAGAUAGAAAUGAUU
1589- UUCAAAGUUGGAAUUGGAGUU
2042- AAUUCUCAUCCAAGAAGCCUU
2450- UUACUCAGAGCUUUGGAUCUU

5' CGUCGAAAAGAAAAGUCUCUU
3' UUGCAGCUUUUCUUUCAGAG

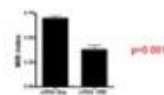
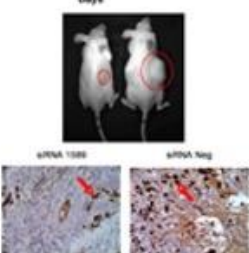
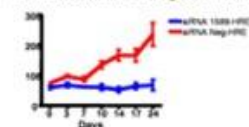


siRNA injections significantly reduce Hif-1 activity in vivo



$p < 0.01$

HIF-1α reduction inhibits tumor growth in vivo



$p < 0.001$

Gillespie and Jensen RL:Methods in Mol Biol: 487:283-301, 2009.



Summary and Conclusions

- Hemangioblastomas
 - Cerebellar
 - Spinal
- Endolymphatic sac tumors
- Treatment
 - Surgery
 - SRS
- Research
 - HIF-1a



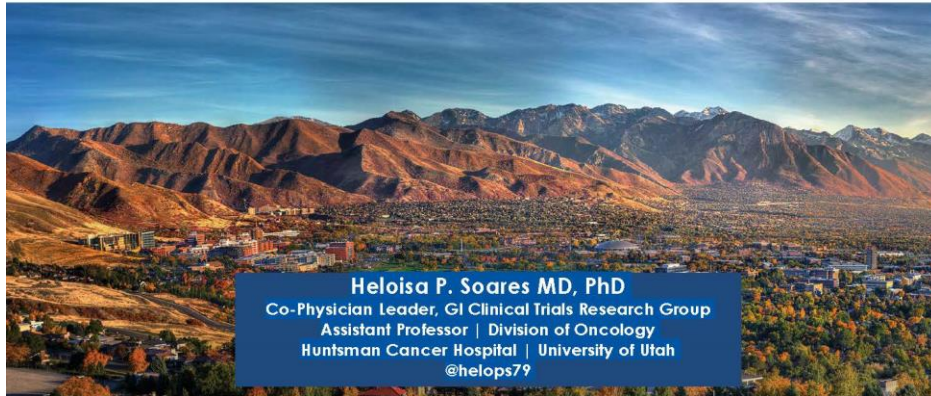
2020 Annual VHL Family Meeting
October 24, 2020

**VHL and Endocrine
Tumor Susceptibility**

Heloisa Soares, MD

2020 VHL Alliance Annual Family Meeting

VHL and Endocrine Tumor Susceptibility



Heloisa P. Soares MD, PhD

Co-Physician Leader, GI Clinical Trials Research Group
Assistant Professor | Division of Oncology
Huntsman Cancer Hospital | University of Utah
@helops79



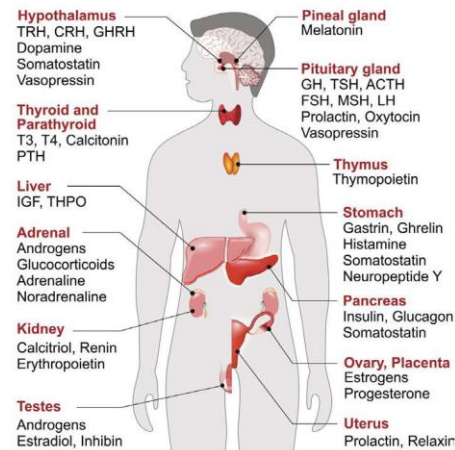
Disclosures

Consulting/Advisory board for Ipsen, Lexicon, Natera, QED Therapeutics, Advanced Accelerator Applications and Exelixis

Let's first understand what is Endocrinology

Endocrinology is the study of hormones and the glands that secrete hormones

HORMONES



Von Hippel-Lindau

- Von Hippel-Lindau (VHL) disease is an autosomal dominant disorder mutations in the *VHL* tumor suppressor gene
- Because of this mutation, tumors can develop in tissues that have expression of this gene, including in endocrine cells:
 - Pancreas - Pancreatic neuroendocrine tumors
 - Adrenal glands - pheochromocytomas,
 - Other nerve tissues - extra-adrenal paragangliomas (rare)

Genotype–phenotype associations in patients with VHL disease

VHL-disease subtype	Genotype	Phenotype
I	VHL exon deletion or truncation usually present	Increased risk of all tumor types; low risk of pheochromocytoma
IIA	VHL exon missense mutation usually present (codon 98)	Associated with a high risk of pheochromocytoma , and retinal and CNS hemangioblastomas
IIB	VHL exon missense mutation usually present	High risk of pheochromocytoma , and retinal and CNS haemangioblastomas, as well as RCC, pNET , and pancreatic cysts
IIC	VHL exon missense mutation usually present (codon 168)	Characterized by increased susceptibility to pheochromocytoma only

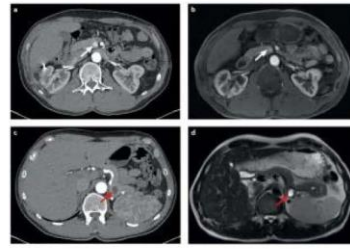
Pancreatic NETs and VHL

- **Pancreatic lesions are common** in VHL disease and often present with benign cystic disease including microcystic or serous adenomas, which occur in up to **70% of patients with VHL**
- Pancreatic NETs have been described in 10% to 17% of patients with VHL disease
- Pancreatic NETs are diagnosed in patients with VHL disease is lower than in sporadic cases (35 versus 58 years)
 - probably due to periodic screening in these patients and may contribute to the better prognosis observed for VHL-associated NETs when compared to sporadic ones
- Pancreatic NETs associated with VHL disease are often **multiple** and are located throughout the pancreas, but mostly in the head of the pancreas
- Vast majority of these pancreatic NETs are **nonfunctional tumors**

Pancreatic NETs: symptoms and diagnosis

Symptoms:

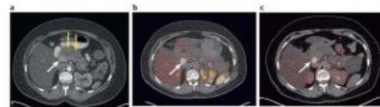
- Most of the time no specific symptoms
- If symptoms: abdominal pain, jaundice, pancreatitis, or even gastrointestinal bleeding and hormonal manifestations are seen



Nature Reviews | Clinical Oncology

Diagnosis:

- CT scans with pancreas protocol, MRIs
- Ga-68 DOTATATE PET-CT
- Pancreas Endoscopic Ultrasound

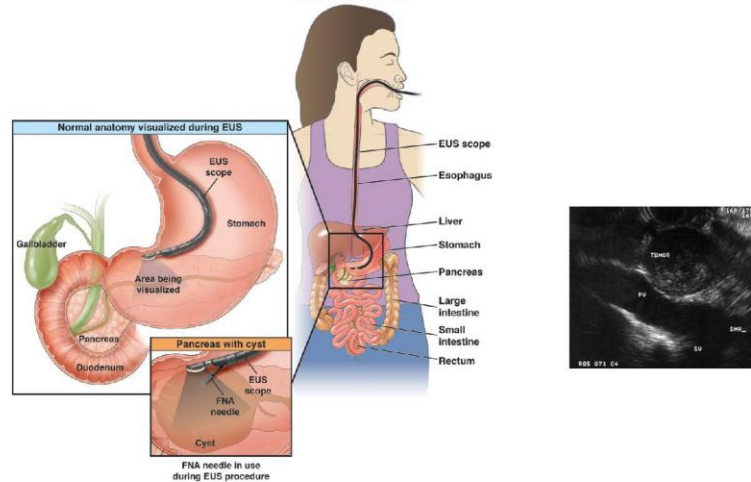


Nature Reviews | Clinical Oncology

Kebebew, E. et al. (2016) *Nat. Rev. Clin. Oncol.*

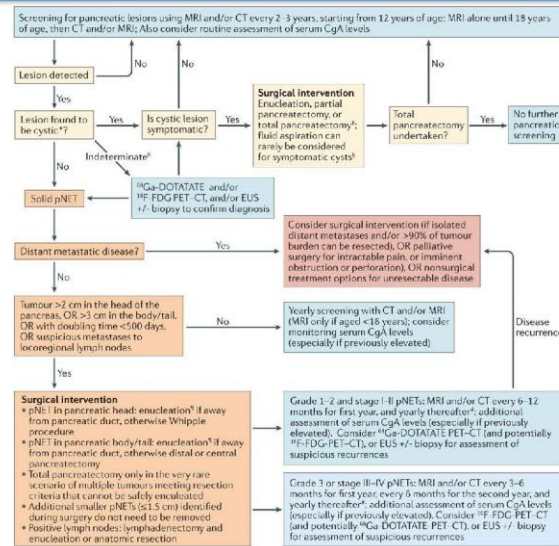
What is a EUS?

Patient undergoing endoscopic ultrasound



Clinical Gastroenterology and Hepatology 2019 17DOI: (10.1016/j.cgh.2019.04.021)

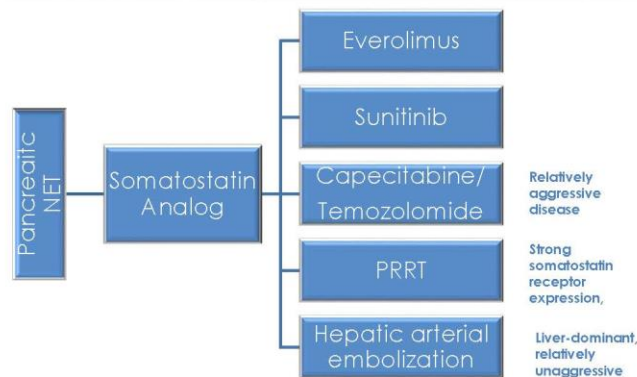
Management algorithm for patients with von Hippel–Lindau disease and pancreatic lesions : expert recommendations



Nature Reviews | Clinical Oncology
Kebebew, E. et al. (2016) Nat. Rev. Clin. Oncol.

Treatment options for advanced-stage pNETs in patients with VHL

Extent of disease	Surgical intervention	SSA	Drug therapy*	TACE	SIRT	PRRT	OLT
Locally advanced (lymph-node metastasis and/or invasion of adjacent organ(s))	If >90% tumour burden can be resected	Consider [†]	Consider [†]	No	No	Consider [†]	No
Unresectable primary tumour	For intractable pain or imminent obstruction or perforation	Consider [†]	Consider [†]	No	No	Consider [†]	No
Distant metastasis	If >90% tumor burden can be resected	Consider [†]	Consider [†]	Consider [†]	Consider [†]	Consider [†]	No
Isolated liver metastases	If completely resectable, also consider RFA/MWA	Consider [†]	Consider [†]	Consider [†]	Consider [†]	Consider [†]	Selectively



Adrenal Gland, Pheochromocytoma and VHL

- Adrenal Medulla hormones are controlled by the nervous system
- When stress or fear is sensed, brain sends signal down sympathetic nervous system to adrenal medulla
- Signal causes the adrenal medulla to release epinephrine (adrenaline) and norepinephrine (noradrenaline) to the rest of the body

Epinephrine

- Stimulates heart rate to increase so more blood can go to muscles
- Allows liver to release sugar to raise blood sugar
- Increases sweating

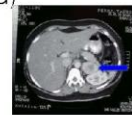
Norepinephrine

- Works with epinephrine
- Constricts blood vessels to raise the blood pressure

Pheochromocytoma and VHL



- Arise from the adrenal medulla and lead to catecholamine excess
- Frequency in up to 20% of VHL patients
- Mean age of diagnosis is 30 yrs old (ranging from 5 to 58 yrs old)
- They can be bilateral and occasionally multifocal.
- Risk of malignancy (eg spread to other organs) is about 10%
- Recent study demonstrated that VHL-related pheo patients are more likely to be young, asymptomatic and normotensive and to have small, multifocal, normetanephrine-secreting tumors.



(Li SR et al: World J Surg 44, 570–577, 2020)

Pheos that develop outside of the adrenal glands are called paragangliomas (paras) and are very rare, even in VHL patients

Pheochromocytoma and VHL: symptoms and Diagnosis

Symptoms

- mostly due to catecholamines production
- High blood pressure
- Rapid or forceful heartbeat
- Profound sweating without any reason
- Severe, throbbing headache
- Tremors
- Paleness in the face
- Shortness of breath
- Sensation of panic
- Anxiety or sense of doom
- Abdominal pain
- Constipation
- Weight loss



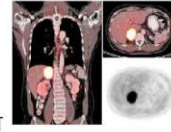
Diagnosis

Anatomical imaging

- ✓ CTs
- ✓ MRIs

Functional Imaging

- ✓ ¹⁸F-DOPA-PET/CT
- ✓ FDG-PET/CT,
- ✓ ¹²³I-MIBG
- ✓ ⁶⁸GaDOTATATE PET/CT



Biochemical

- ✓ plasma metanephrine
- ✓ Plasma normetanephrine
- ✓ less commonly: urine metanephrine/normetanephrine

Treatments of Pheochromocytoma

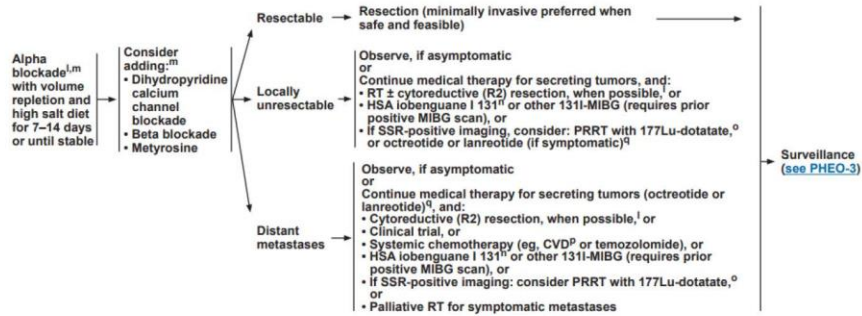
- For localized disease, surgical resection is indicated
- Perioperative management of pheochromocytomas

Combination of alpha-adrenergic and beta-adrenergic blockade is necessary to prevent catecholamine-mediated life-threatening complications such as cardiac arrhythmias, hypertensive crisis, and myocardial infarction.

Category	Drug	Dosing	Common Side Effects
Nonselective alpha-blocker	Phenoxybenzamine	10 mg given 2–3 times per day (up to 60 mg daily)	Orthostatic hypotension, nasal congestion, tachycardia
	Phentolamine	Intravenous 2.5–5 mg boluses	
Selective alpha-1 blockers	Doxazosin	2–4 mg given 2–3 times per day	Orthostatic hypotension, dizziness, tachycardia
	Prazosin	1–2 mg given 2 times per day	
	Terazosin	1–4 mg given once daily	
Dihydropyridine calcium channel blockers	Nicardipine	30 mg 2 times per day	Headache, edema
	Amlodipine	5–10 mg once daily	
Tyrosine hydroxylase inhibitor	Metyrosine	250–500 mg titrated up to 4 times per day	Severe fatigue, extrapyramidal neurologic side effects, nausea
Selective beta-1 blocker only after full alpha-blockade	Metoprolol	25–100 mg given 2 times per day	Fatigue, dizziness, asthma exacerbation
Nonselective beta-blocker only after full alpha-blockade	Propranolol	20–40 mg given 2–3 times per day	Fatigue, dizziness, asthma exacerbation

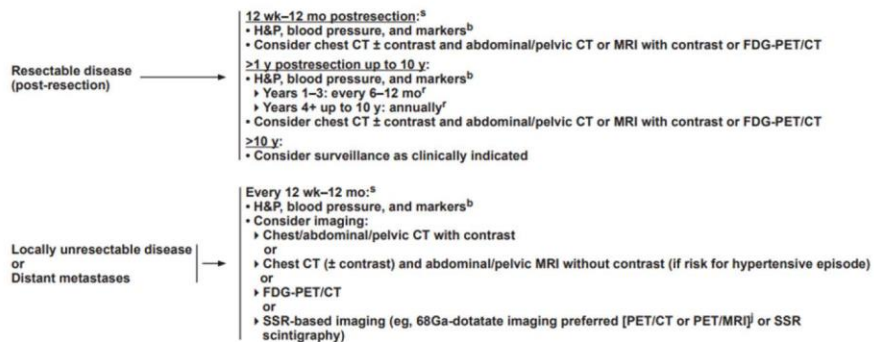
Fishbein L: Hematol Oncol Clin N Am 30 (2016) 135–150

Treatments of Pheochromocytomas: NCCN Guidelines



Surveillance of Pheochromocytomas: NCCN Guidelines

SURVEILLANCE^{h,f}



Screening recommendations in patients with VHL

Surveillance Modality (Tumors being screened)	AGE ¹						Pregnancy ¹¹
	<5 years	Beginning at age 5y	Beginning at age 11y	Beginning at age 15y	Beginning at age 30y	Beginning at age 65y ¹	
History and Physical Examination²	Yearly from age 1 year	Yearly	Yearly	Yearly	Yearly	Yearly	Prior to conception ¹¹
Blood Pressure and Pulse (Pheochromocytomas/paragangliomas)	Yearly from age 2 years	Yearly	Yearly	Yearly	Yearly	Yearly	Prior to conception ¹¹
Dilated Eye Examination³ (Retinal Hemangioblastomas)	Every 6-12 months, beginning before age 1 year	Every 6-12 months	Every 6-12 months	Every 6-12 months	Yearly	Yearly	Prior to conception, then Every 6-12 months ¹¹
Metanephrines⁴ (Pheochromocytomas/paragangliomas)	—	Yearly	Yearly	Yearly	Yearly	Stop routine ¹	Prior to conception ¹¹
MRI Brain and Spine w/wo Contrast^{5,6,7} (CNS Hemangioblastomas)	—	—	Every 2 years ⁸	Every 2 years ⁸	Every 2 years ⁸	Stop routine ¹	Prior to conception ¹¹
Audiogram (Endolymphatic sac tumors)	—	—	Every 2 years	Every 2 years	Every 2 years	Stop routine ¹	—
MRI Abdomen w/wo Contrast^{5,6,7} (Renal cell carcinomas, Pheochromocytomas/paragangliomas, Pancreatic neuroendocrine tumors/cysts)	—	—	—	Every 2 years ⁸	Every 2 years ⁸	Stop routine ¹	Prior to conception ¹¹
MRI Internal Auditory Canal¹⁰ (Endolymphatic sac tumors)	—	—	—	Once	—	—	No specific changes

Thank you!



Heloisasoares@hci.utah.edu

Twitter: @helops79

2020 Annual VHL Family Meeting
October 24, 2020

**Retinal Findings
in VHL**

Eric Hansen, MD

RETINAL CAPILLARY HEMANGIOBLASTOMA IN VON HIPPEL-LINDAU

Eric Hansen MD
Assistant Professor of Ophthalmology and Visual Sciences
John A. Moran Eye Center
University of Utah



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CASE:

40 yo man referred for retinal lesions noted in the right eye

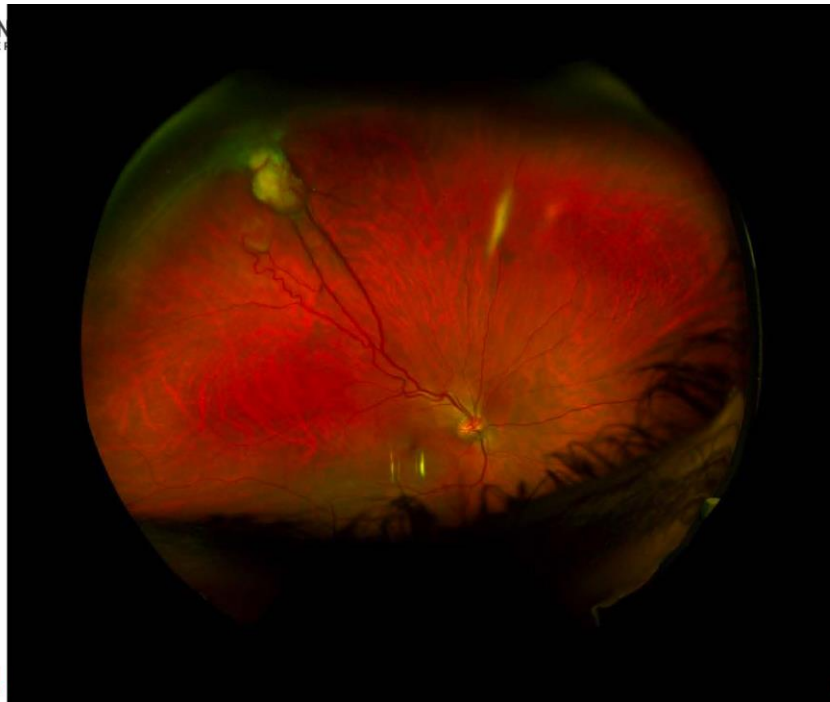
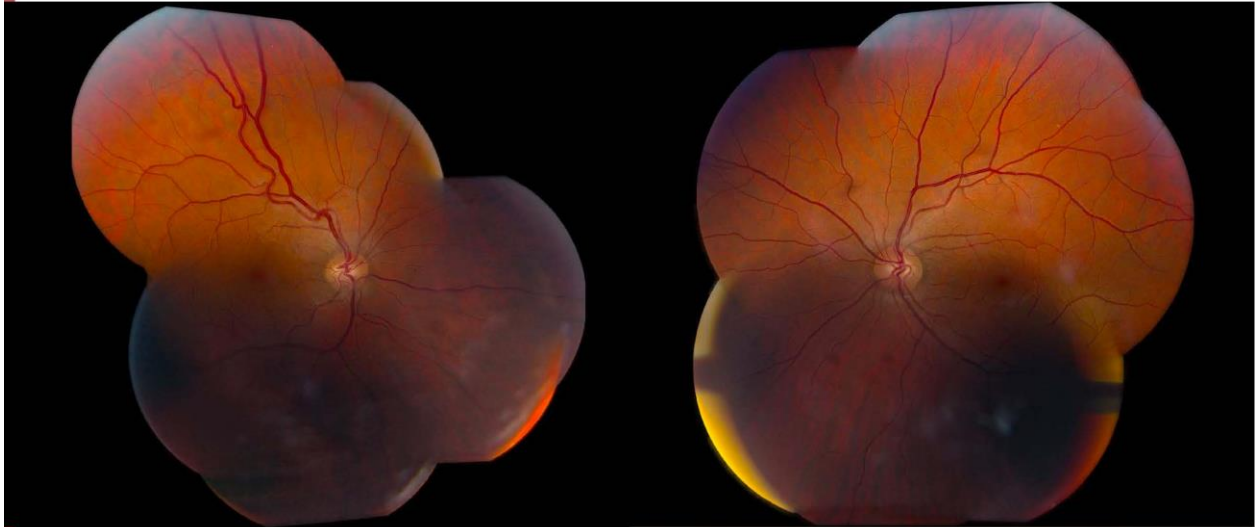
- No visual or ocular symptoms
- No previous ocular history
- Last exam was 2 years ago

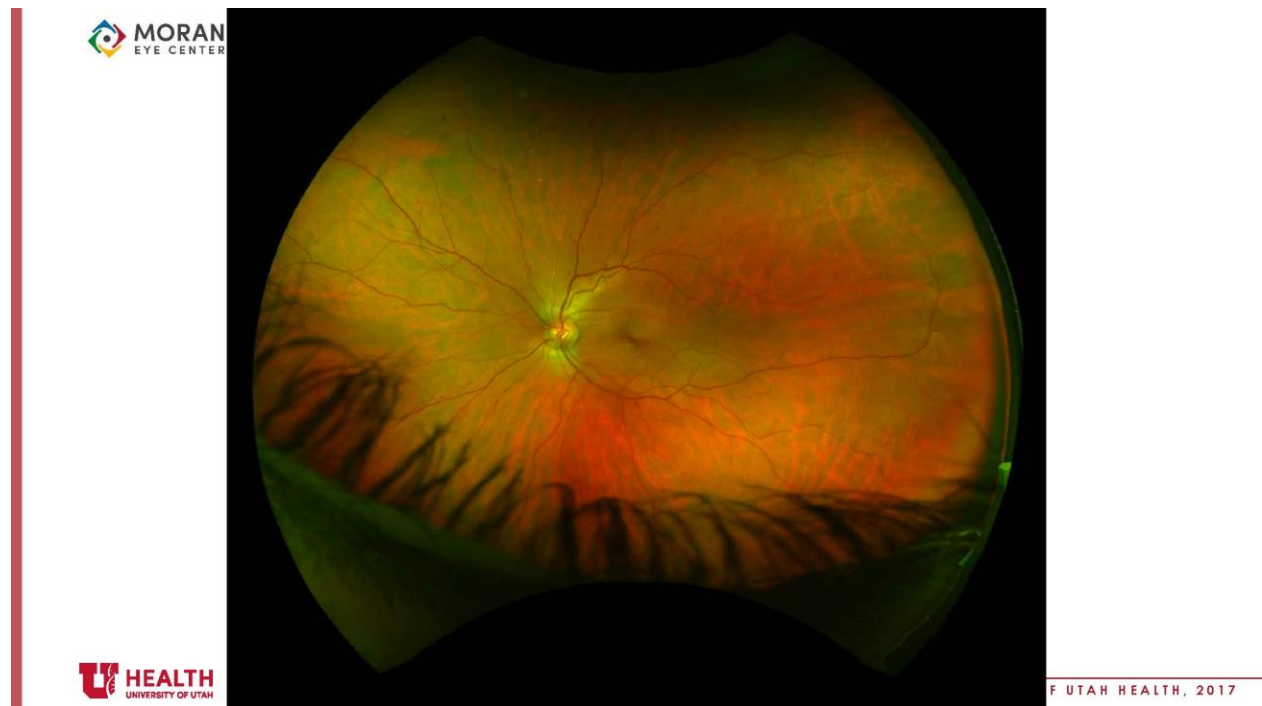
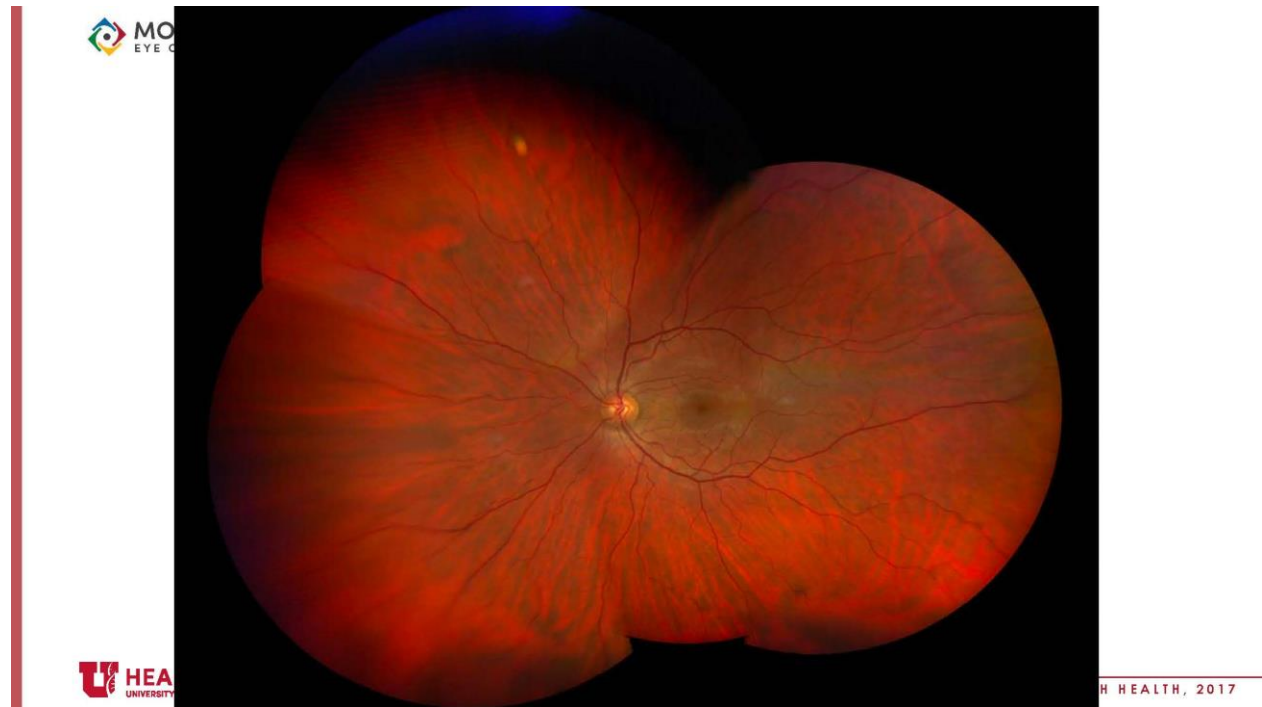
- Vision: 20/20 both eyes
- IOP: normal both eyes
- Motility: Full both eyes
- Visual Fields: Full both eyes

- Anterior segment:

Slit Lamp and Fundus Exam

External Exam		
	Right	Left
External	Normal	Normal
Slit Lamp Exam		
	Right	Left
Lids/Lashes	Normal	Normal
Conjunctiva/Sclera	White and quiet	White and quiet
Cornea	Clear	Clear
Anterior Chamber	Deep and quiet	Deep and quiet
Iris	Round and flat	Round and flat
Lens	Clear	Clear





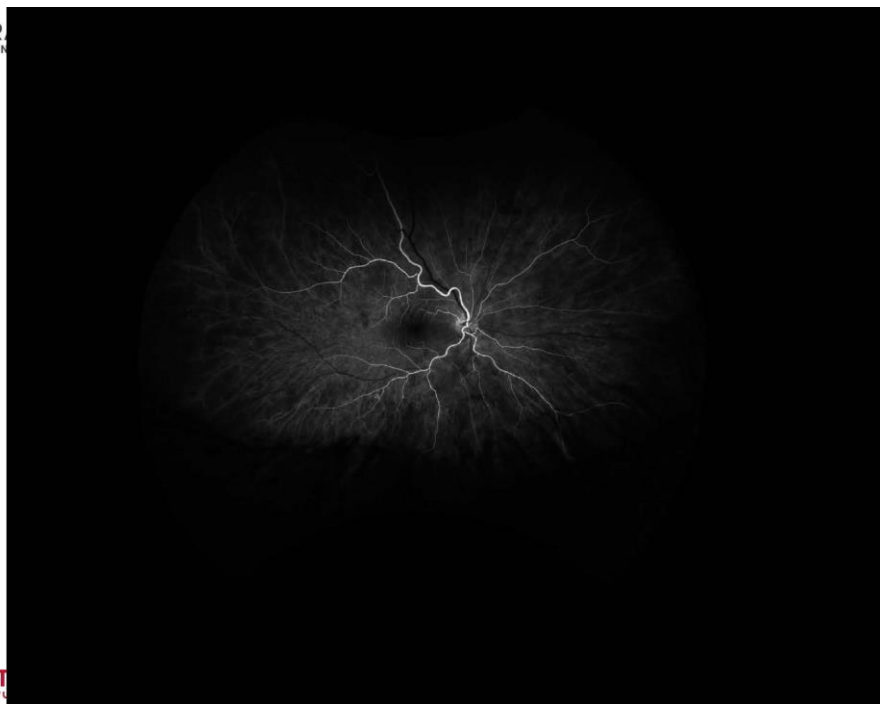
Next Step?

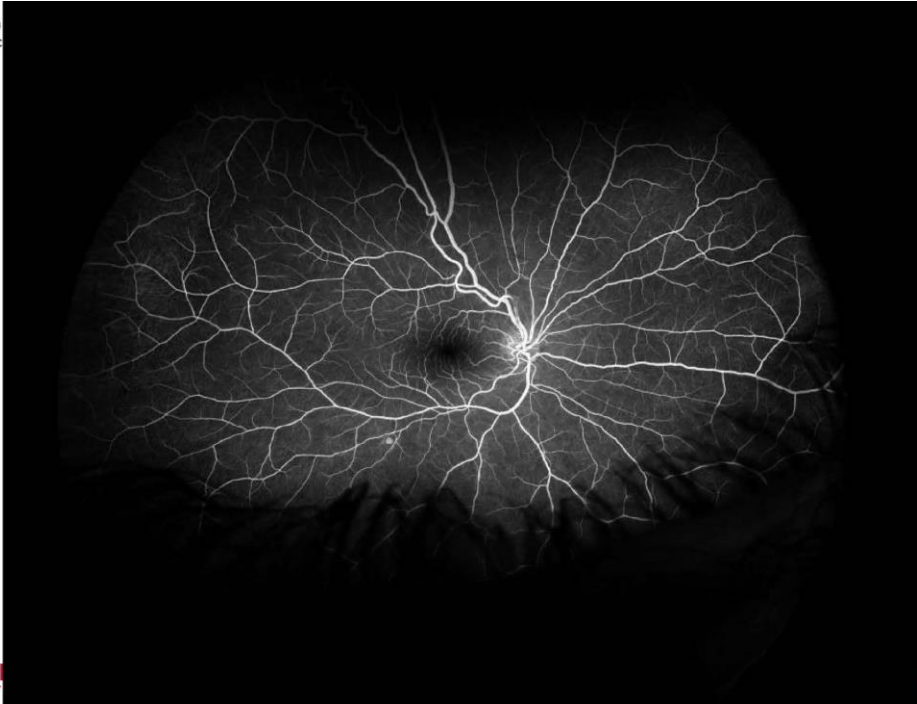


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 MORAN
EYE CENTER



NEXT STEPS:

- Additional History:
- Family History:
- Workup:
 - Ophthalmic Imaging ✓
 - Referral for:
 - Neuro-imaging
 - Abdominal imaging
 - Medical management
 - Genetic testing & counseling

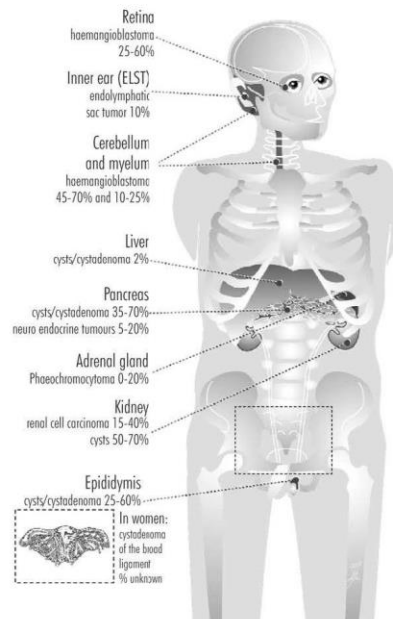
Hx of neurosurgical
resection of cerebellar
hemangioblastoma

- Mother died of Renal Cell Carcinoma
- No known FH of VHL

Von-Hippel Lindau

MULTISYSTEM DISEASE

- Autosomal dominant, multisystemic cancer syndrome
 - ❖ Benign and malignant
- Mutation in VHL gene
- 1/36,000
- 95% penetrance



Hes et al 2005

VHL GENE

- Tumor suppressor gene
- Chromosome 3 (3p25-26)
- Codes for pVHL, important for oxygen sensing

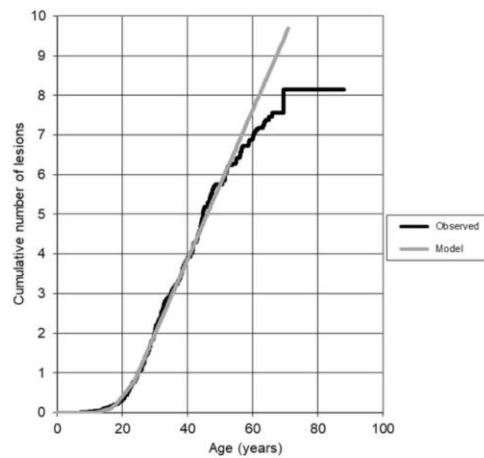
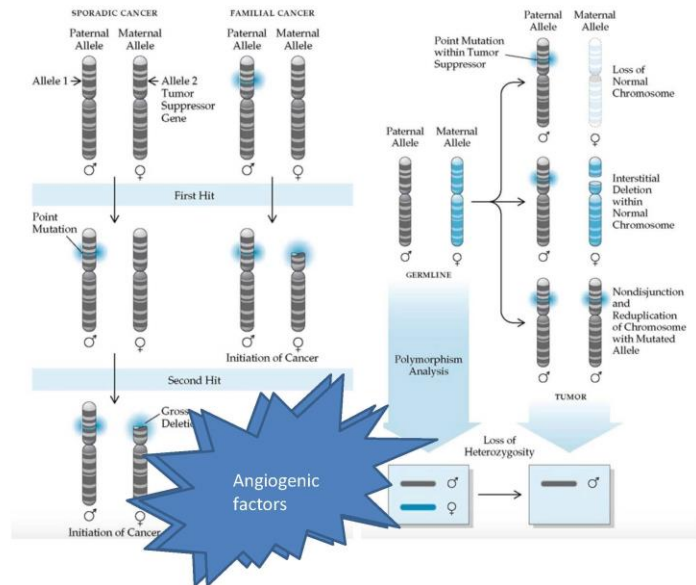


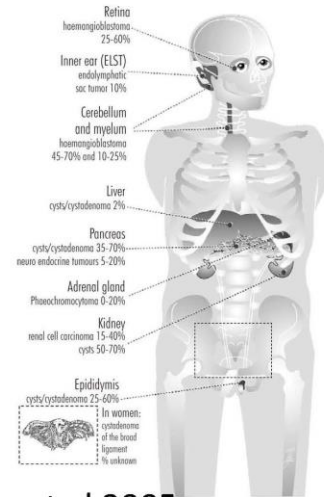
Fig. 2 Average cumulative number of VHL-related manifestation during life in VHL mutation carriers summated for all organs; Poisson model (grey line) versus observed data (black line)

van der Horst-Schrivers et al 2019

- (+) family history with one of:
 - RCH
 - CNS hemangioblastoma
 - Pheochromocytoma
 - Clear cell renal carcinoma
- (-) family history with:
 - 2 or more central nervous system hemangioblastomas (**RCH counts!**)
 - One CNS lesion and one visceral tumor (RCC or Pheo)
- **Genetic testing**

+FH -> 1

-FH -> 2



Hes et al 2005



Table 1

Genotype-phenotype correlation for von Hippel-Lindau disease and possible responsible pathophysiological mechanism

Type VHL	Type of VHL gene germline mutation	Retinal HAB	CNS HAB	RCC	PHAEO	Mechanisms for VHL mediated tumorigenesis
1	missense microdeletions insertions splice site nonsense large deletions	+	+	+	-	loss of function (i.e. HIF-1α degradation)
2A	missense	+	+	-	+	gain of function (PHAEO)
2B	missense	+	+	+	+	loss of function (HAB+RCC)
2C	missense	-	-	-	+	gain of function, fibronectin

Type 1: no pheo
Type 2: Missense, + pheo

HAB, haemangioblastoma; CNS, central nervous system; RCC, renal cell carcinoma (clear cell type); PHAEO, pheochromocytoma; HIF, hypoxia-inducible factor; +, tumour present; -, tumour absent

Hes et al 2005

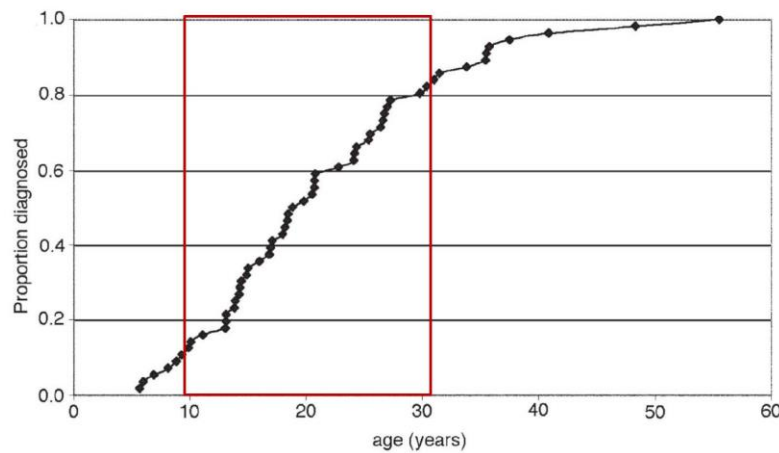
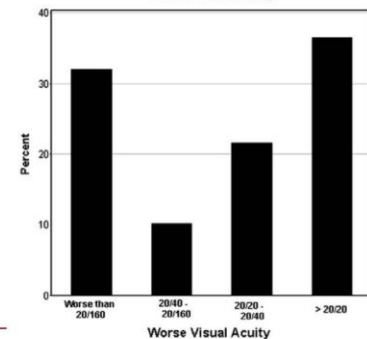
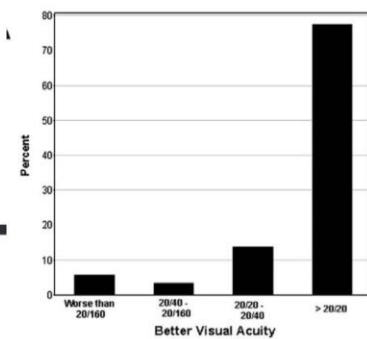


Figure 1. Graph of the cumulative age at onset curve in 57 patients with retinal angiomatosis in von Hippel-Lindau disease.

Clinical Characterization of Retinal Capillary Hemangioblastomas in a Large Population of Patients with von Hippel-Lindau Disease

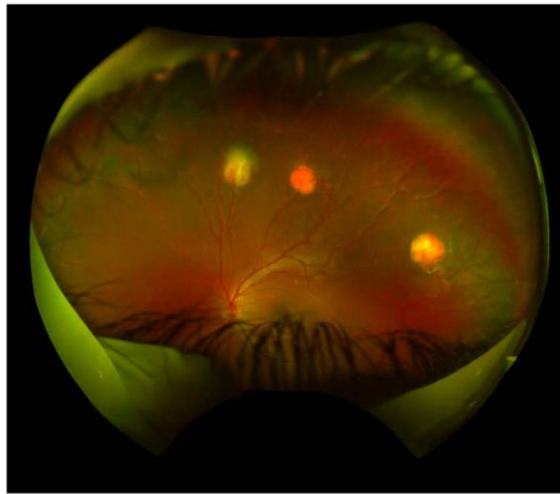
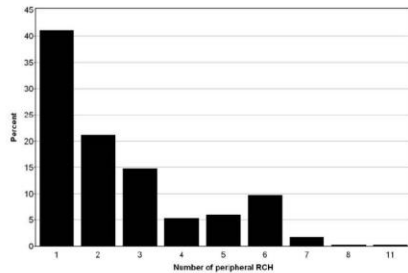
Wai T. Wong, MD, PhD,¹ Elvira Agrón, MS,¹ Hanna R. Coleman, MD,¹ Tam Tran, BS,¹ George F. Reed, PhD,¹ Karl Csaky, MD,² Emily Y. Chew, MD¹

- 335 patients
- 50-60% Bilateral
- Visual impairment associated with:
 - Age
 - Juxtapapillary lesions
 - Size and #

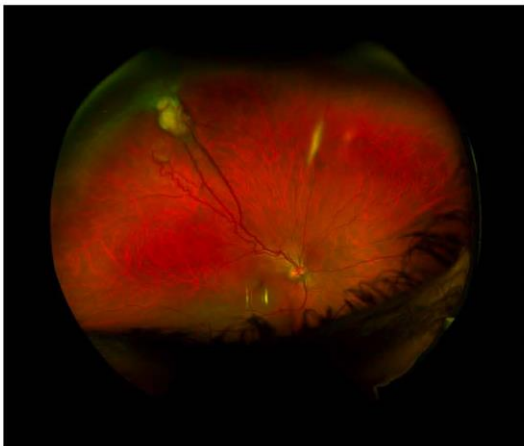


ONE'S COMPANY, TWO'S A CROWD, THREE'S A PARTY

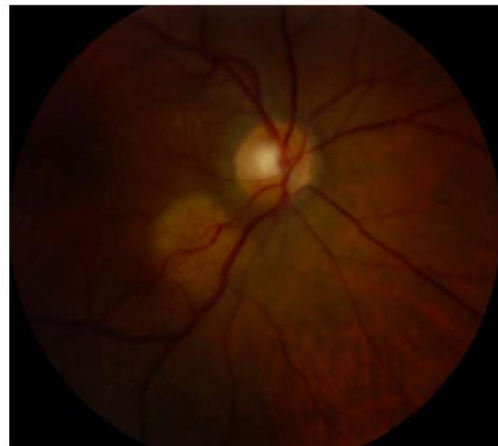
- Solitary vs multifocal
 - Screen even if solitary and unilateral
 - Younger if VHL



LOCATION, LOCATION, LOCATION



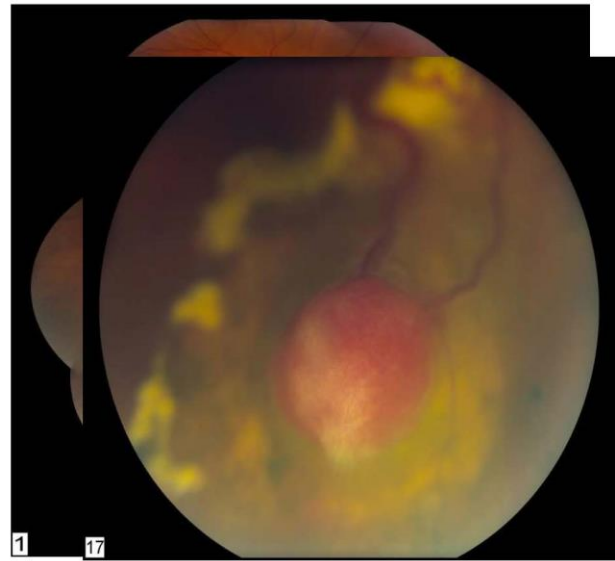
85% peripheral



15% juxtapapillary

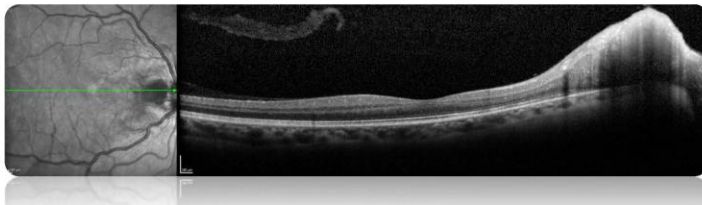
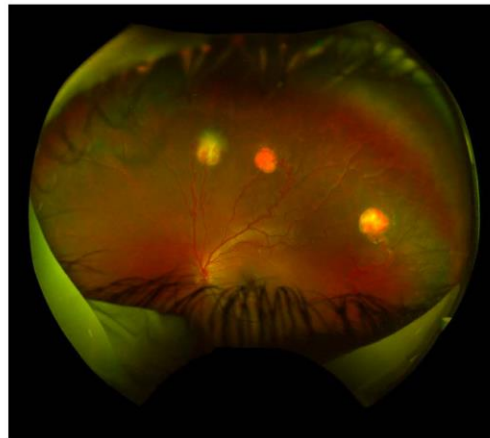
VISION LOSS

- Visual impairment is common:
 - 25% of extrapapillary RCH
 - 65% juxtapapillary
- Two major causes of vision loss:
 1. Exudation and edema
 2. Gliosis and traction

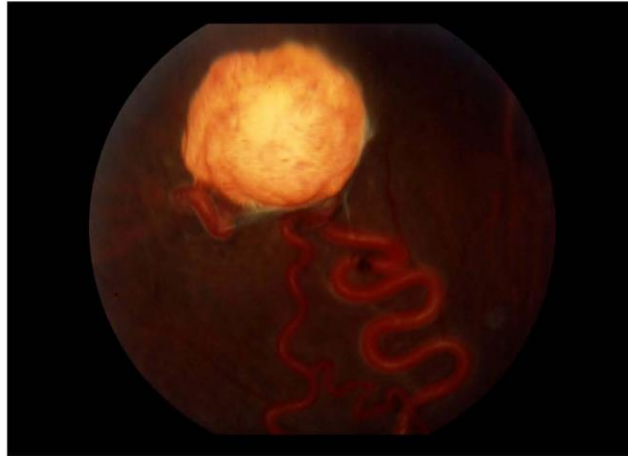


IMAGING FEATURES:

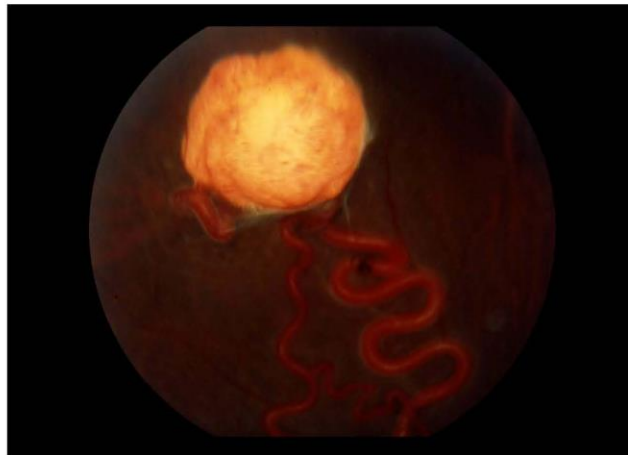
- Nodular gray-red or orange intraretinal lesion
- Feeder and drainage vessel
- Exudation
 - Intraretinal edema
 - Subretinal fluid
 - Lipid exudates
- Early hyperfluorescence with late leakage
 - Useful for identifying early lesions
- On OCT, hyper-reflective lesion of inner retina that can displace outer retina retinal layers with growth



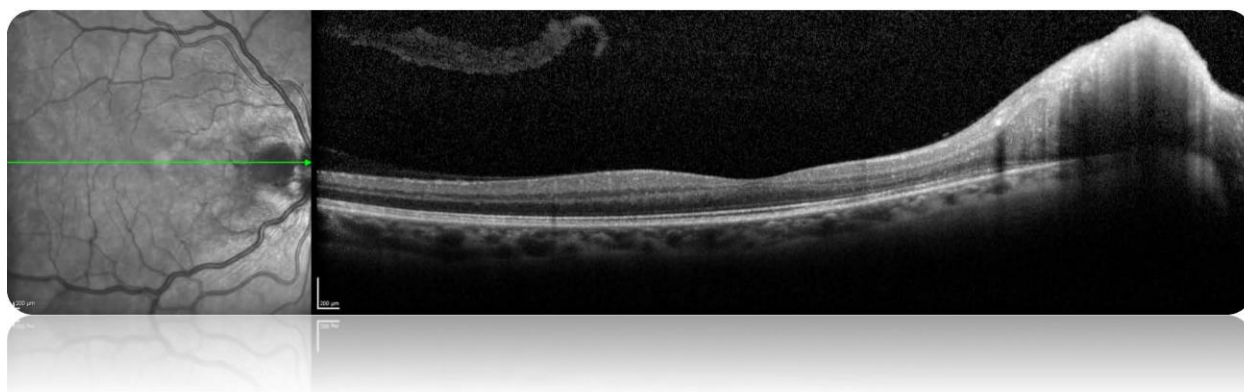
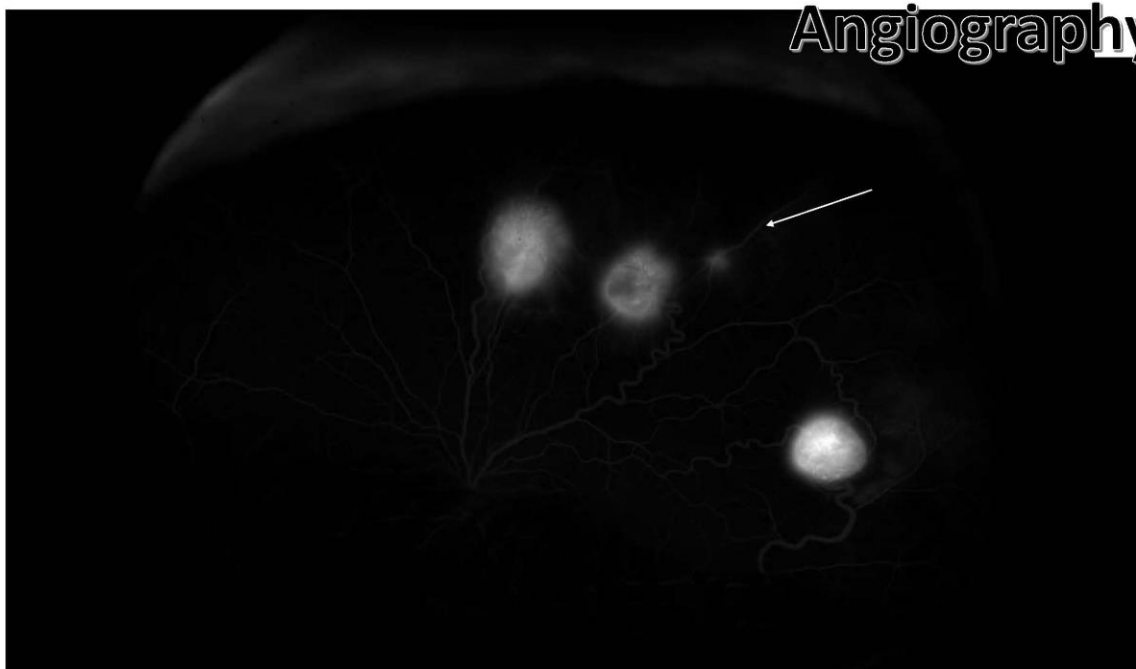
NODULAR, GREY-RED OR ORANGE LESION



FEEDER AND DRAINAGE VESSEL



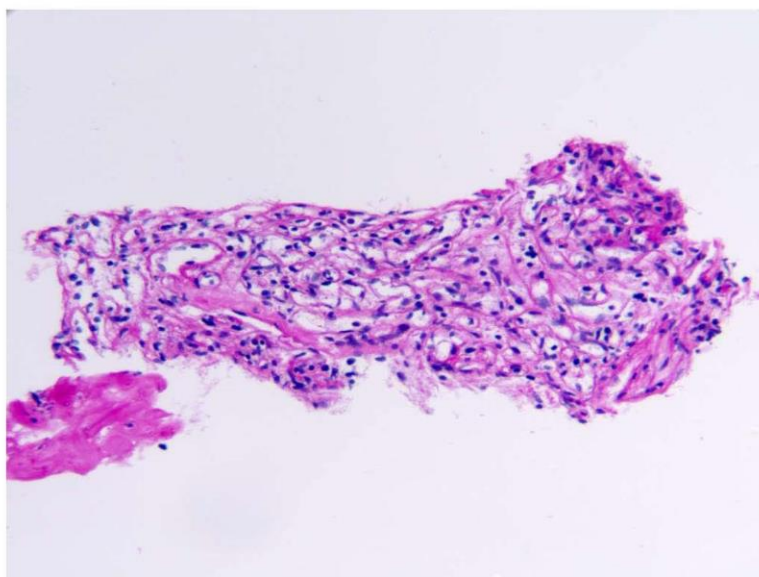
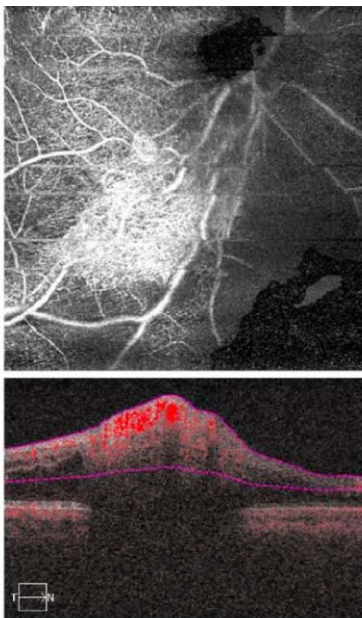
Angiography:

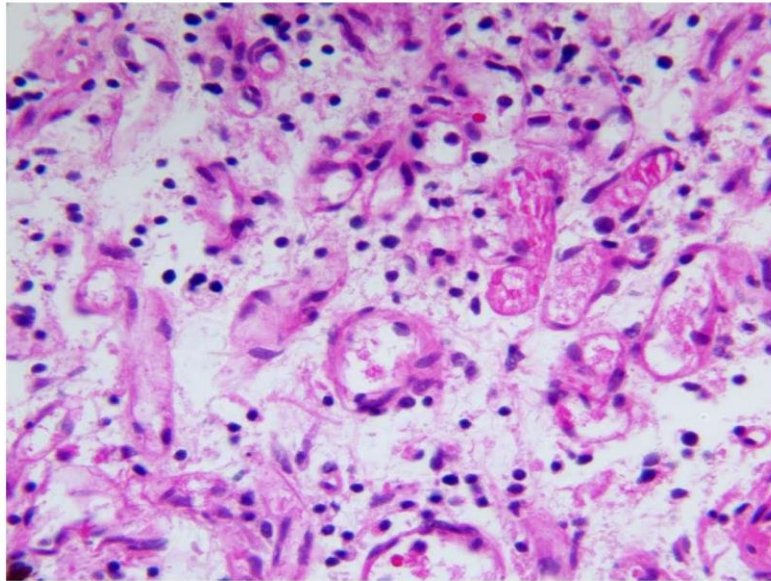


OCT

Hyper-reflective inner retina lesion displacing outer retina retinal layers with growth

OCT- ANGIOGRAPHY





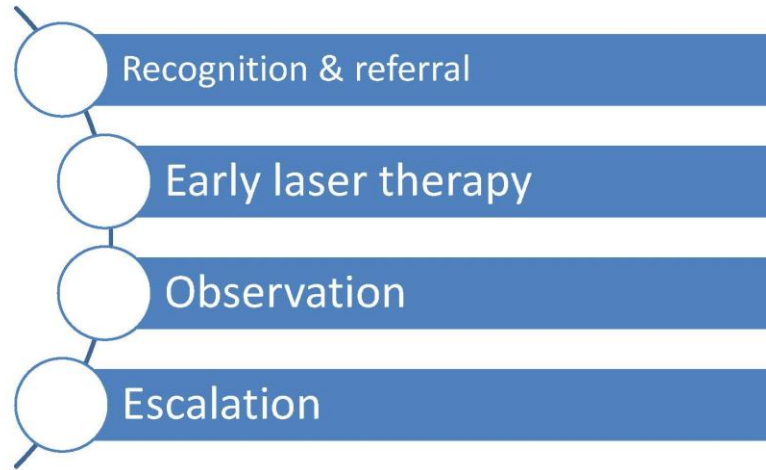
Credit: Dr Dubovy, Bascom Palmer Eye Institute

TREATMENT MODALITIES

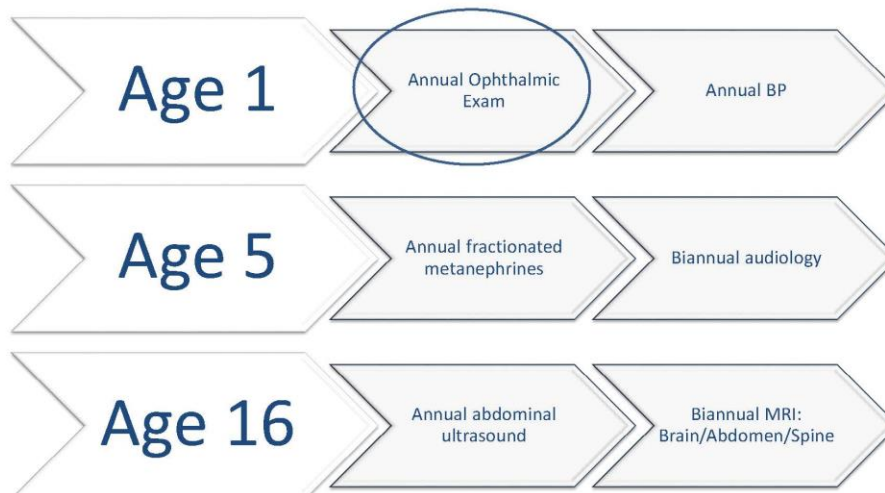
- Laser
- Cryotherapy (freezing)
- Photodynamic Therapy
- Radiation
- Intravitreal injections
- Surgery and resection

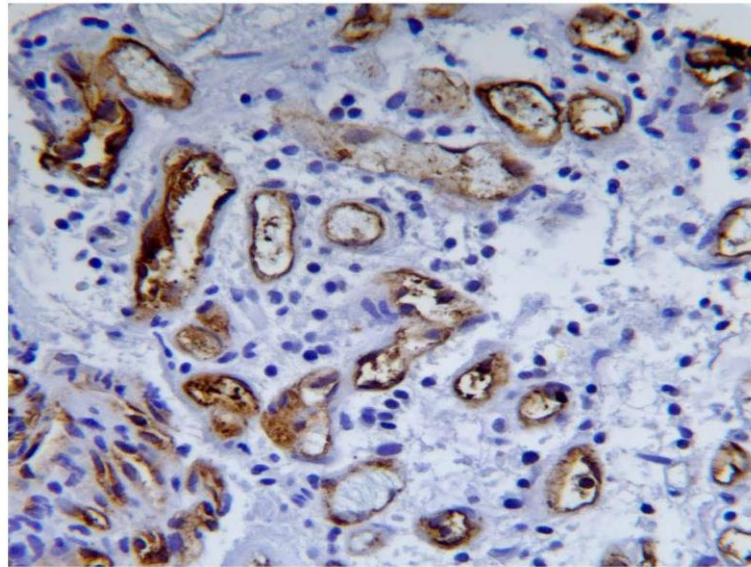


CORE PRINCIPLES



SCREENING





LASER TREATMENT

- Mainstay of treatment
- Long duration, yellow wavelength Argon
- Multiple sessions with lower energy
- Titrated to induce capillary closure and stop leakage



12/11/2013
13

Not original data

PHOTODYNAMIC THERAPY

- Juxtapapillary or maculopapillary bundle tumors
- Control of exudation (leaking)
- Partial tumor regression in 50% of eyes



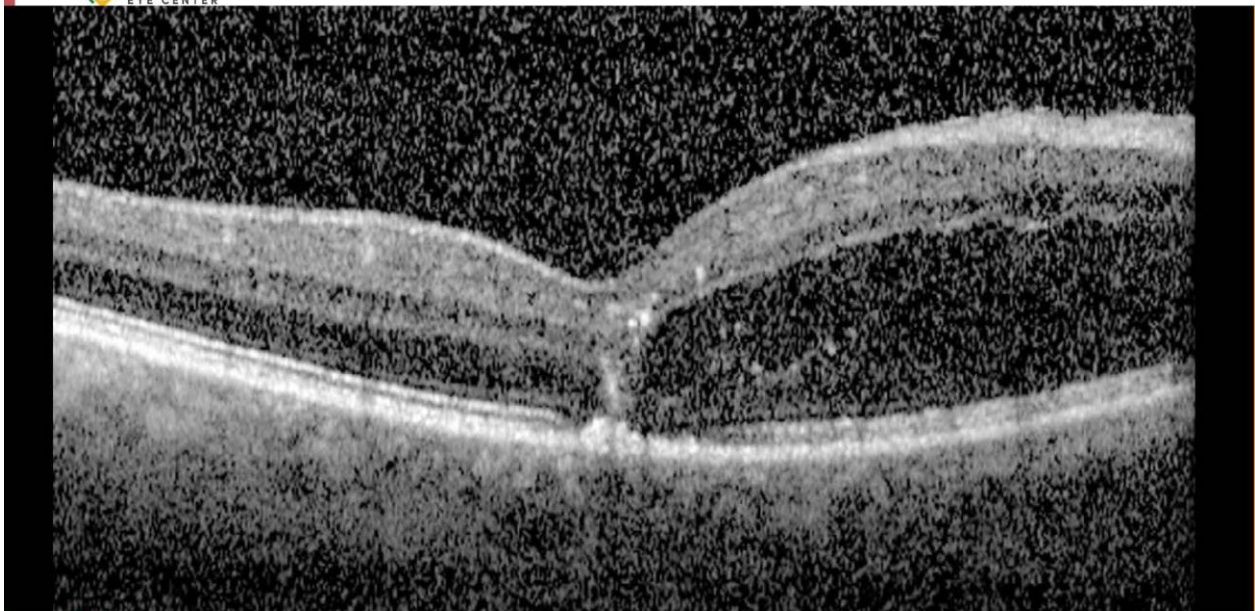
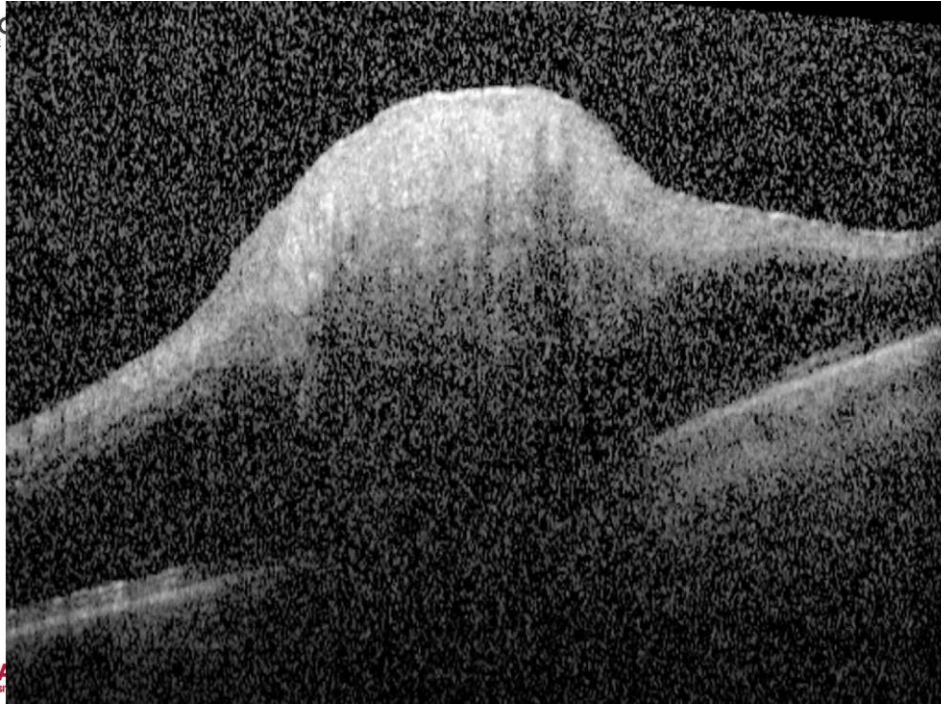
JUXTAPAPILLARY HEMANGIOBLASTOMA

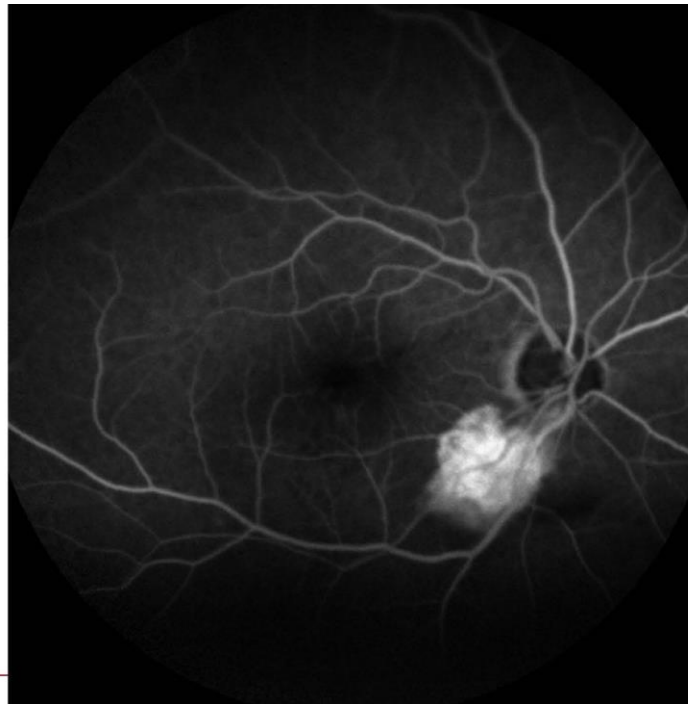
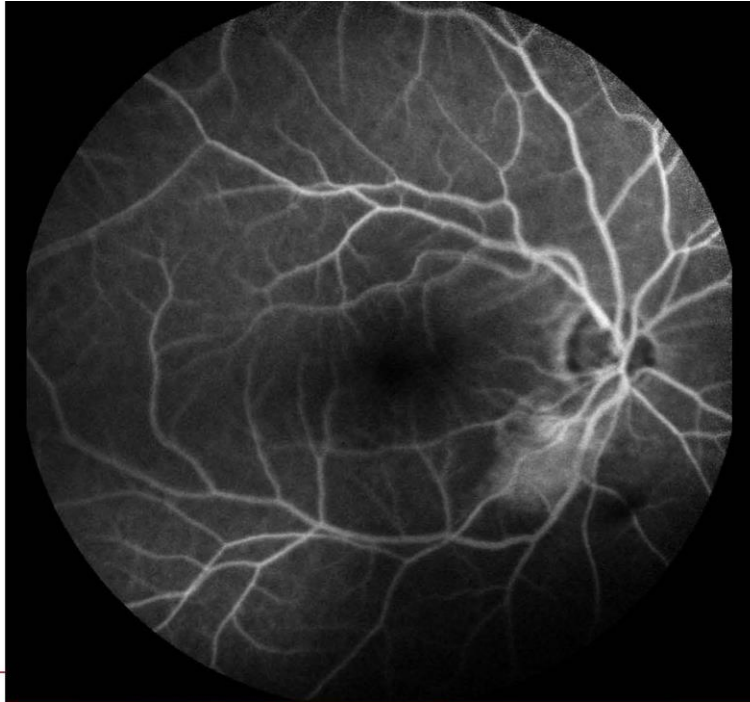


TREATMENT OF JUXTAPAPILLARY RCH

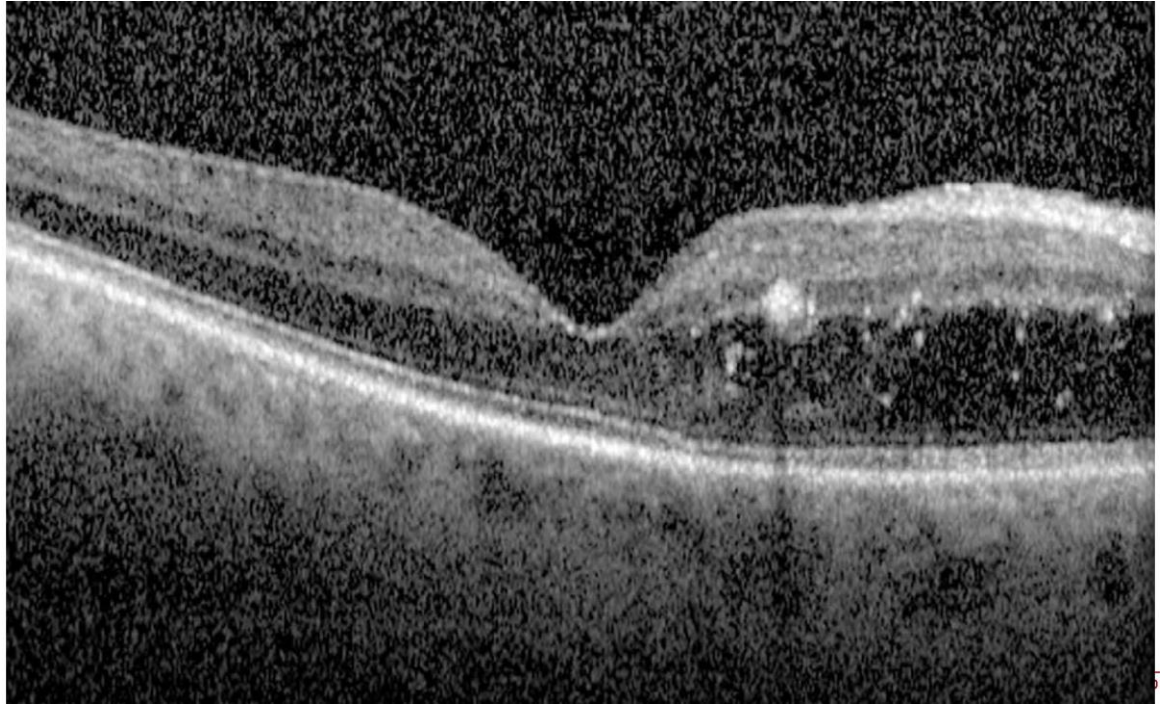
- Observation
- PDT
- Intravitreal anti-vegf or steroids
- Titrated laser photocoagulation





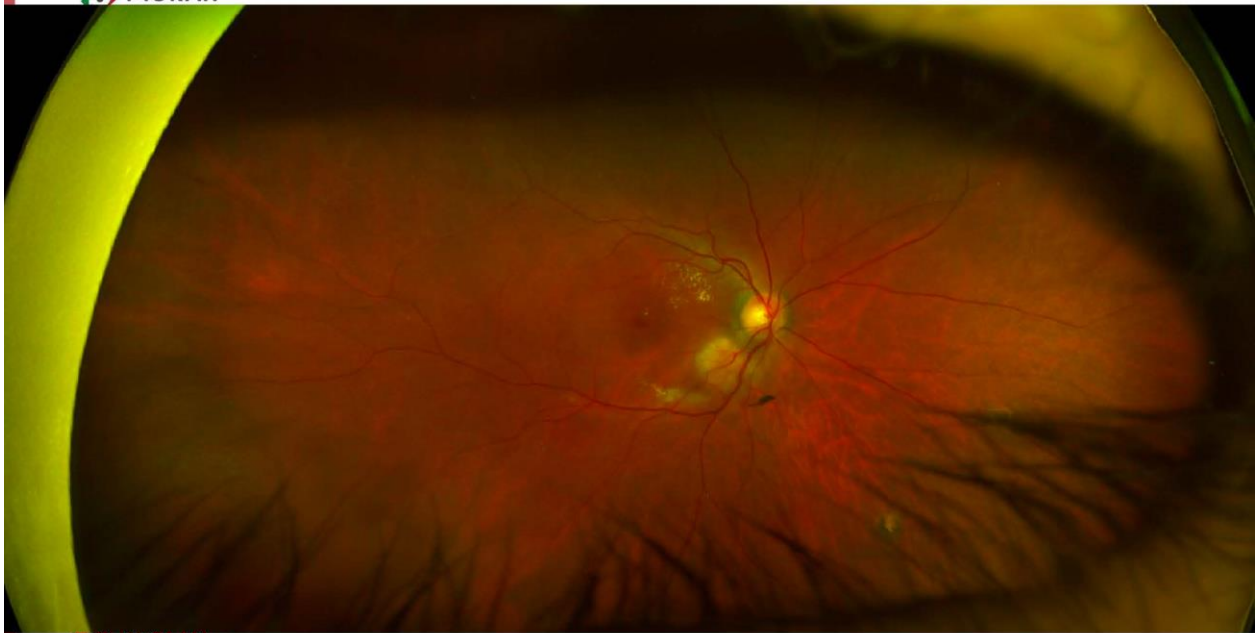






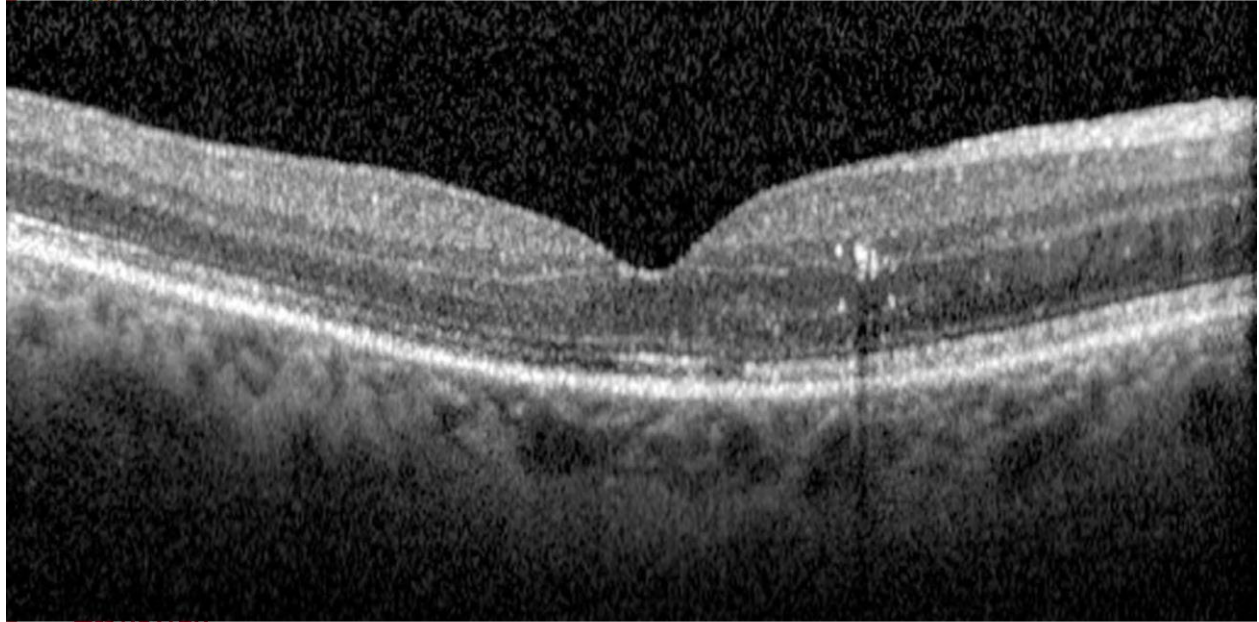
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 MORAN



 **HEALTH**
UNIVERSITY OF UTAH

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VITREORETINAL SURGERY FOR PATIENTS WITH SEVERE EXUDATIVE AND PROLIFERATIVE MANIFESTATIONS OF RETINAL CAPILLARY HEMANGIOBLASTOMA BECAUSE OF VON HIPPEL-LINDAU DISEASE

REMZI AVCI, MD,* SAMI YILMAZ, MD,* UMIT UBEYT INAN, MD,† BERKANT KADERLI, MD,‡
SADIK GORKEM CEVIK, MD§

LARGE TUMORS

- Cryo:
 - Carries inflammation risk
- PDT and argon laser:
 - Sometimes less effective
- Radiation
 - Brachytherapy
 - EBRT
- Surgery
 - Vitrectomy

Salvage External Beam Radiotherapy of Retinal Capillary Hemangiomas Secondary to von Hippel-Lindau Disease

Visual and Anatomic Outcomes

Deepak Raja, MD,¹ Matthew S. Benz, MD,¹ Timothy G. Murray, MD,¹ Erika M. Escalona-Benz, MD,¹ Arnold Markoe, MD²

Objective: To examine the visual and anatomic outcomes of patients with retinal capillary hemangiomas secondary to von Hippel-Lindau (VHL) disease treated with globe-sparing fractionated external beam radiotherapy (EBRT) after progression of hemangiomas despite initial therapy.

Design: Retrospective noncomparative consecutive case series.

Participants: Review of medical records of 5 patients with retinal capillary hemangiomas secondary to VHL disease.

Intervention: External beam radiotherapy delivered to a total dose of 2160 cGy given over 12 daily fractions.

Main Outcome Measures: Data on visual acuity and tumor size were collected at baseline, 1, 3, 6, and 12 months after EBRT, and at final follow-up, using echography, fundus photographs, and clinical examination.

Results: Six eyes of 5 patients were treated. Mean follow-up was 26.3 months (range, 6–51). Mean baseline visual acuity was 20/70. Mean visual acuity at last follow-up was 20/45 (range, 20/25–20/60). Tumor volume reduction was 27.5 mm³ (range, 0.9–109.6 mm³). Mean percentage reduction in tumor volume was 39.6% (range, 3.3%–71.1%).

Conclusions: External beam radiotherapy is a useful option in the treatment of retinal hemangiomas secondary to VHL disease that progress despite standard therapy. External beam radiotherapy leads to improvement in visual acuity, reduction in tumor volume, and stabilization of retinal detachment in most patients treated. *Ophthalmology* 2004;111:150–153 © 2004 by the American Academy of Ophthalmology.

Ramiah et al

2019

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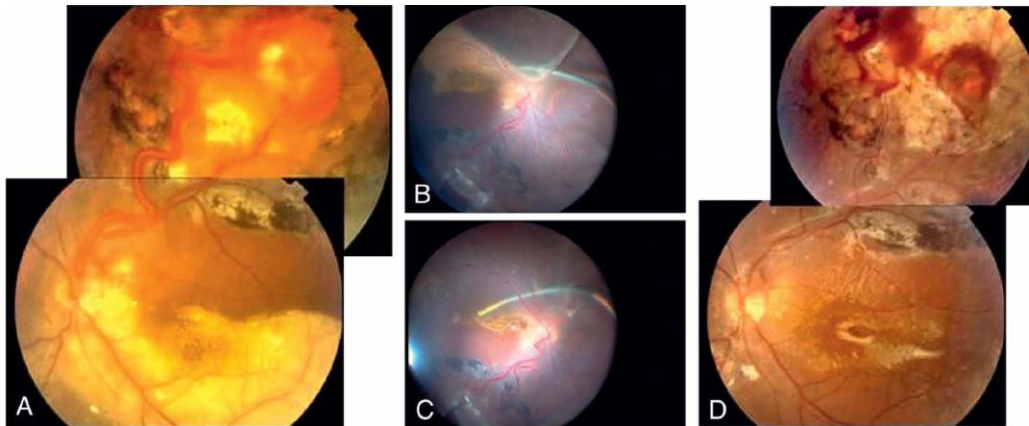
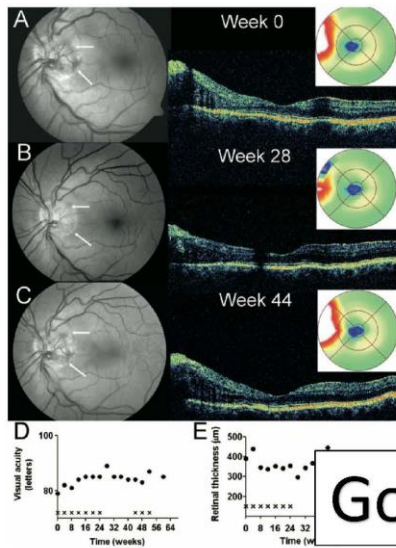


Fig. 3. In a 28-year-old man (Patient 8), visual acuity was 20/400 preoperatively and 20/80 postoperatively at the final visit. Twenty-three-gauge vitrectomy was performed. Follow-up period was 26 months. **A.** In this image obtained before surgery, laser scars, hemangioma, macular hard exudates, and dilated feeder vessels are seen. **B.** Subretinal macular hard exudates were aspirated with subretinal aspiration needle after retinotomy. **C.** All exudates on macular region are seen to be removed. **D.** Fundus view at postoperative 2 months is seen; note the regressed feeder vessels and clear macular region.



ROLE OF ANTI-VEGF THERAPY

Intravitreal Ranibizumab Therapy for Retinal Capillary Hemangioblastoma Related to von Hippel-Lindau Disease

Wai T. Wong, MD, PhD,¹ Katharine J. Liang, BS,² Keri Hammel, MS,¹ Hanna R. Coleman, MD,² Emily Y. Chew, MD²

Purpose: To evaluate the effect of intravitreal ranibizumab on retinal capillary hemangioblastomas (RCHs) associated with von Hippel-Lindau (VHL) disease that are not amenable or responsive to standard therapy.

Design: Prospective, noncomparative, interventional case series.

Participants: Five patients with VHL-associated RCH with exudative changes and visual loss.

Methods: Monthly intravitreal injections of ranibizumab (0.5 mg) were given over a course of 6 months for a total of 7 injections, with additional injections considered until week 52. The final study visit was designated as 8 weeks after the final study injection.

Main Outcome Measures: The primary outcome was the change in best-corrected visual acuity (BCVA) of ≥ 15 letters at the final visit compared with baseline. Secondary outcomes included change in lesion size, exudation as assessed clinically and by fluorescein angiography, change in retinal thickness as evaluated by optical coherence tomography, and adverse event assessments.

Results: Patients received an average of 10.0 ± 3.1 injections over an average period of 47 ± 14 weeks, including follow-up. Mean change in BCVA was a decrease of 9 ± 20 letters, with 1 patient gaining ≥ 15 letters, and 2 patients losing ≥ 15 letters. Changes in both lesion size and exudation were variable.

Conclusions: Intravitreal ranibizumab, delivered as monotherapy every 4 weeks, had minimal beneficial

Good for combined treatment

SYSTEMIC THERAPY

THE LANCET Oncology

Volume 19, Issue 10, October 2018, Pages 1351-1359

Articles

Pazopanib in patients with von Hippel-Lindau disease: a single-arm, single-centre, phase 2 trial

Prof Eric Jonasch MD^{1,2,3,4}, Prof Ian E McCutcheon MD⁵, Prof Dan S Gombos MD⁶, Prof Kamran Akhtar MD⁷, Prof Nancy D Perrier MD⁸, Diane Liu MSc¹, Christine C Robichaux BSN⁹, Mercedes F Villarreal⁹, Justin A Weldon BSc⁹, Ashley H Woodson⁸, Patrick G Pilie MD⁹, Prof Gregory N Fuller MD¹⁰, Prof Steven G Waguespack MD¹, Prof Surena F Matin MD¹

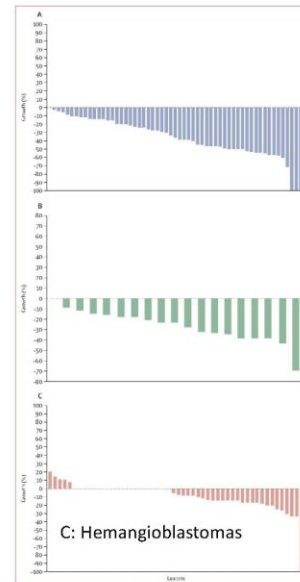


Figure 3 Response by histology type. (A) retinal capillary hemangioblastomas, (B) pancreatic lesions, and (C) hemangioblastomas.

- Underwent laser photocoagulation OU
- Abdominal imaging: **Bilateral Renal cysts**
- Neuro-imaging: **Multiple small hemangioblastomas**
- Genetic testing: **VHL c.481C>T, Type 1**
- Medical screening: (-) metanephrines

2020 Annual VHL Family Meeting
October 24, 2020

Radiology Imaging

Glen Morrell, MD, PhD

Radiology and Von Hippel-Lindau Disease

Glen Morrell, MD, PhD
Department of Radiology and Imaging Sciences
University of Utah

Role of Radiology in VHL

- Find tumors before they metastasize
- Localize tumors for surgical treatment

Tumors associated with VHL

- Hemangioblastomas
 - Spinal cord
 - cerebellum

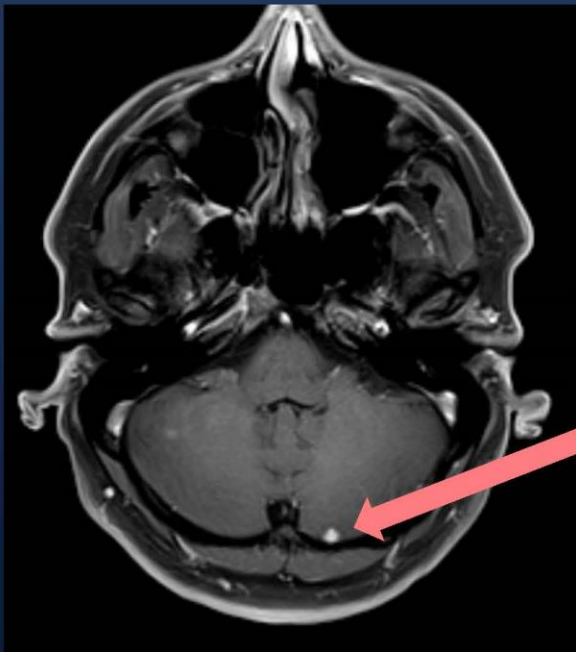


Hemangioblastoma

- Most common tumor associated with VHL, in 60-80% of VHL patients
- Benign (does not metastasize), but occurs in confined spaces → symptoms
 - Headache
 - Loss of coordination
 - Nausea/vomiting
 - Imbalance
 - Weakness or tingling in arms or legs
 - Compromised bowel or bladder function

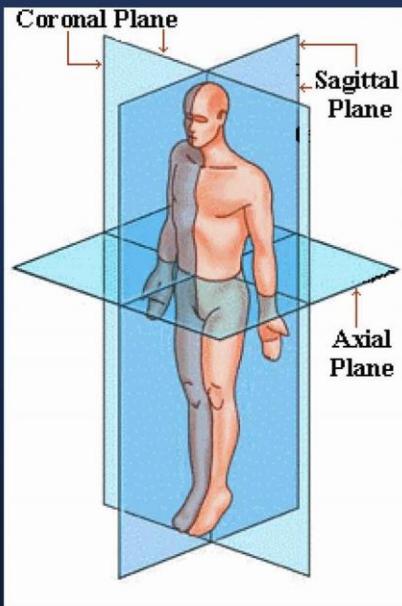
Hemangioblastoma

- Observed until symptomatic, then surgically resected
- Best depicted with MRI of the brain and spine
 - MRI every 2 years or if symptoms occur



Axial image,
Contrast enhanced MRI

Image planes



coronal



sagittal



axial



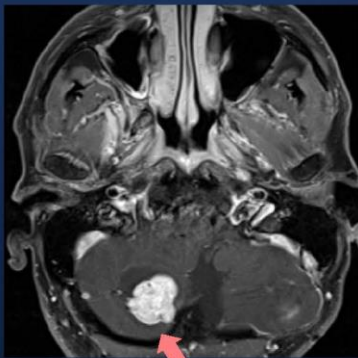
Sagittal image,
Contrast enhanced MRI



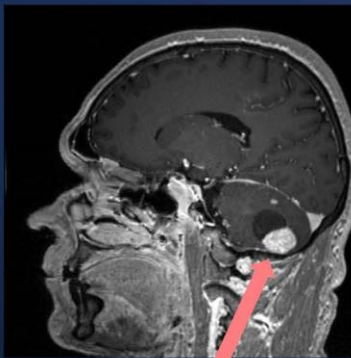
Sagittal image,
Contrast enhanced MRI

Contrast enhanced MRI

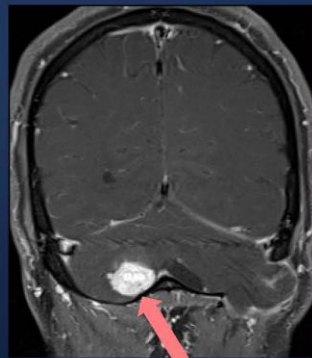
axial



sagittal



coronal



Imaging modalities



ultrasound



CT



MRI

Ultrasound

Pros:

- Rapid hands-on examination
- Harmless – no radiation
- Inexpensive

Cons:

- Can only see where sound can penetrate
- Can't see through air-tissue interfaces
- Can't see deep structures
- Not routinely used for VHL imaging
 - Depiction of renal masses is variable, inconsistent

CT

Pros:

- Rapid
- Widely available
- Coverage of extended area of body
- Good depiction of kidneys, pancreas

Cons:

- Radiation
- Limited tissue contrast

MRI

Pros:

- Superb tissue contrast – especially in brain, spine, kidneys, pancreas
- No ionizing radiation → does not increase risk of cancer

Cons:

- Long exam time
- Claustrophobia
- Limited extent of image volume in head-foot direction
- High cost

Tumors associated with VHL

Retinal hemangioblastoma

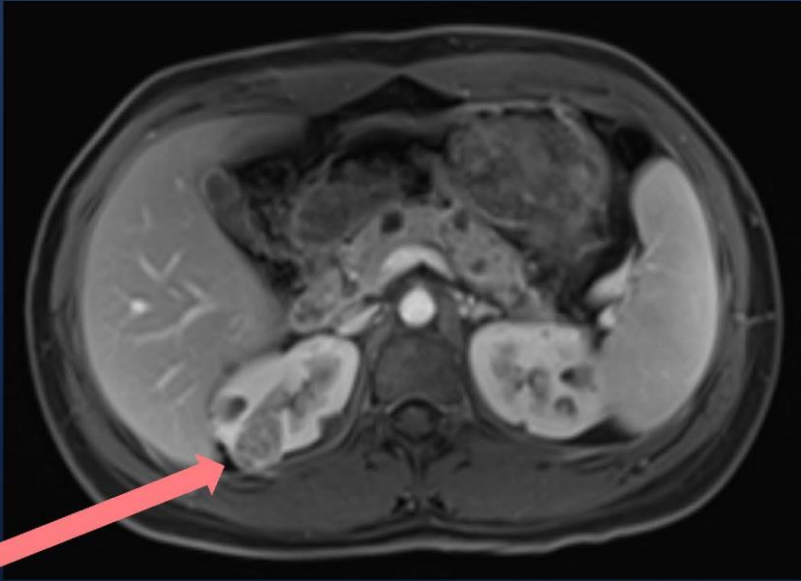
- Up to 60% of VHL patients, median age 21
- Eventually become bilateral
- Can cause blindness in 5-8% of cases
- Treated with laser surgery, 90% success
- Annual eye exam
- No role for radiology



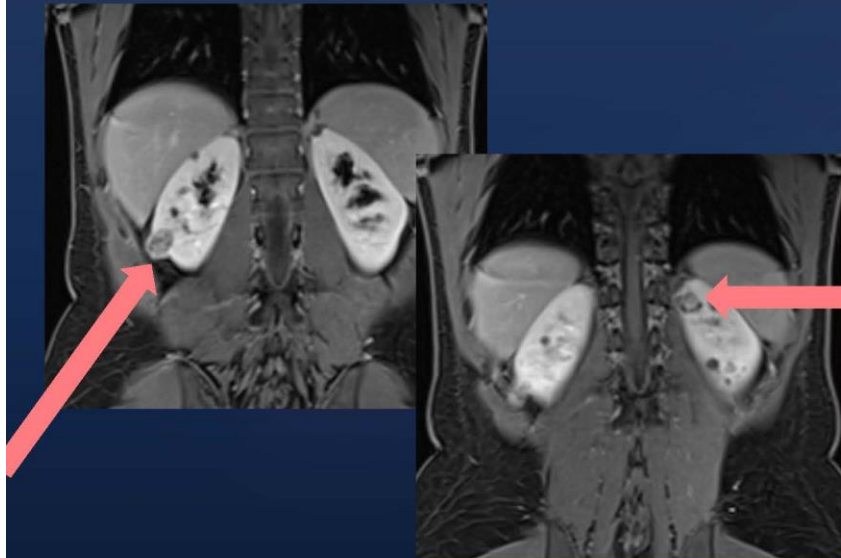
Tumors associated with VHL

Renal Cell Carcinoma (RCC)

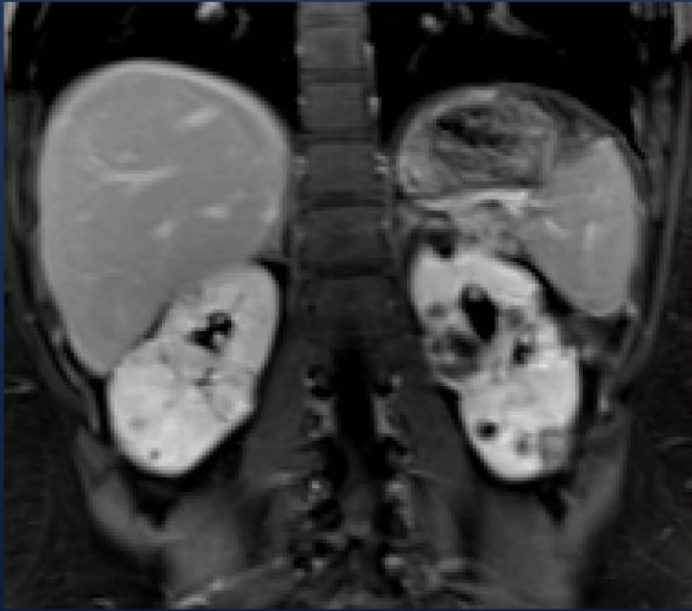
- 30-40% of VHL patients
- 70% have renal cell carcinoma by age 60
- Cancer of the kidney, risk of metastasis
- Treatment is surgical removal or ablation, typically when > 3cm
- Must balance risk of metastasis with accumulating loss of kidney function
 - Dialysis → 42% five year survival
 - Metastatic RCC → 0-20% five year survival
- MRI every two years*



Contrast enhanced MRI
Axial plane
RCC
Incidental pancreatic cysts



Contrast enhanced MRI
Coronal plane
RCC's in both kidneys
Incidental renal cysts

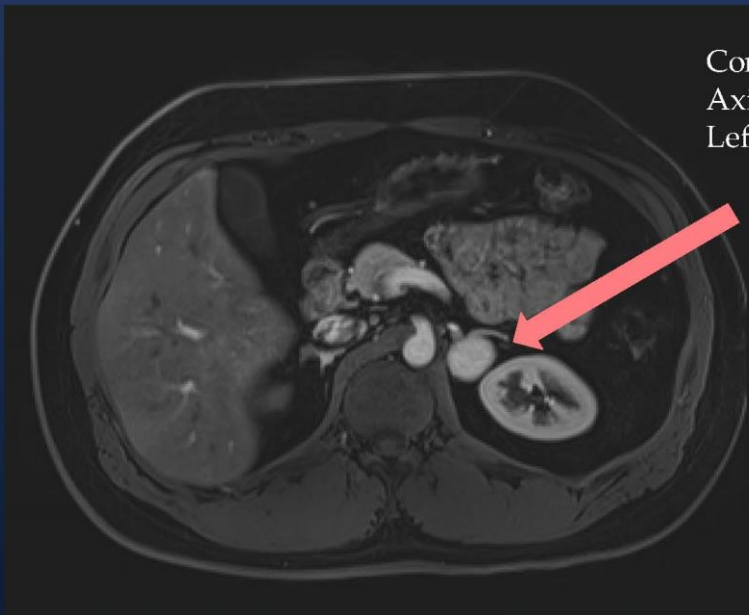


Contrast enhanced MRI
Coronal plane
RCC's in both kidneys
Incidental renal cysts
Partial nephrectomies

Tumors associated with VHL

Pheochromocytoma

- 20% of VHL patients
- Usually in adrenal gland
- Usually benign but can cause symptoms
 - High blood pressure
 - Flushing
 - Racing heart, palpitations
 - Sweating
- Surgically resected
- Annual blood test or 24 hour urine collection



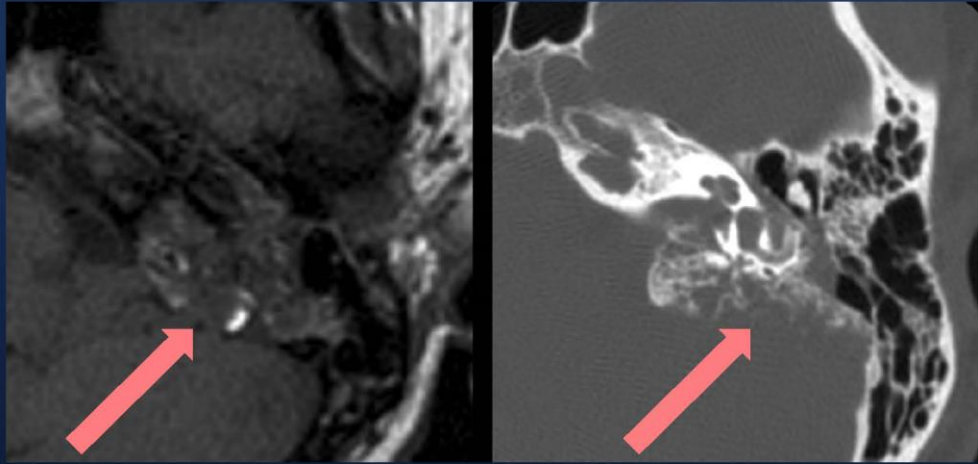
Contrast enhanced MRI
Axial plane
Left adrenal pheochromocytoma

Tumors associated with VHL

Endolymphatic sac tumor (ELST)

- 6-15% of VHL patients
- Median age 31
- Can cause deafness or facial nerve palsy
- Surgery usually curative
- Audiology every 2-3 years or if symptomatic

Non-contrast T1 MRI (left), CT (right)
Axial plane
Endolymphatic sac tumor



Images courtesy of Richard Wiggins MD

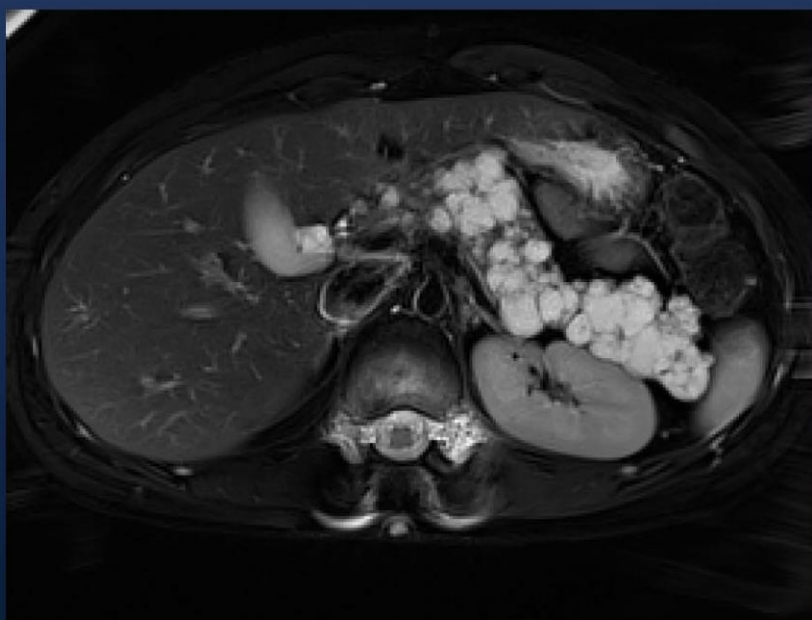
Tumors associated with VHL

Pancreatic tumors

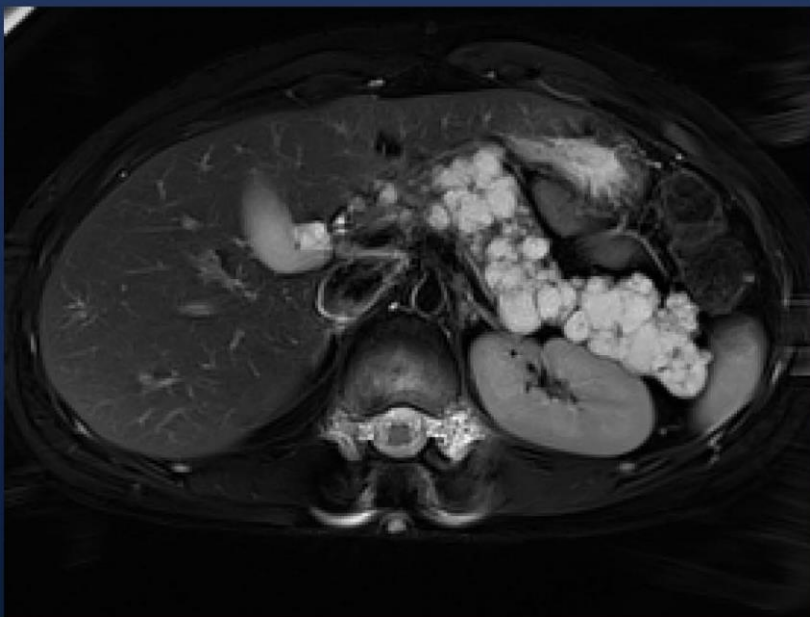
- Benign cysts very common (70% of patients)
- Serous cystadenoma
 - Benign
- Pancreatic neuroendocrine tumor (PNET)
 - Rare
 - Can be malignant in 8% of cases
- MRI every two years



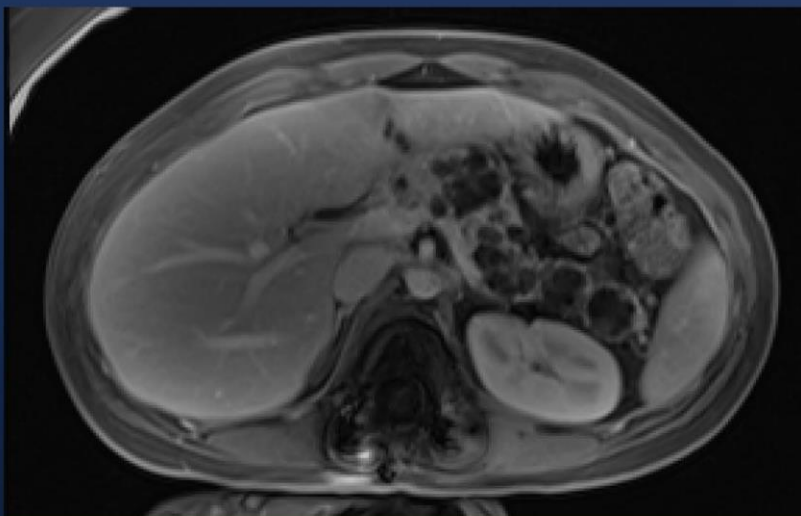
T2-weighted MRI
Axial plane
Pancreatic cyst



T2-weighted MRI
Axial plane
Pancreatic cysts
Possible cystadenoma



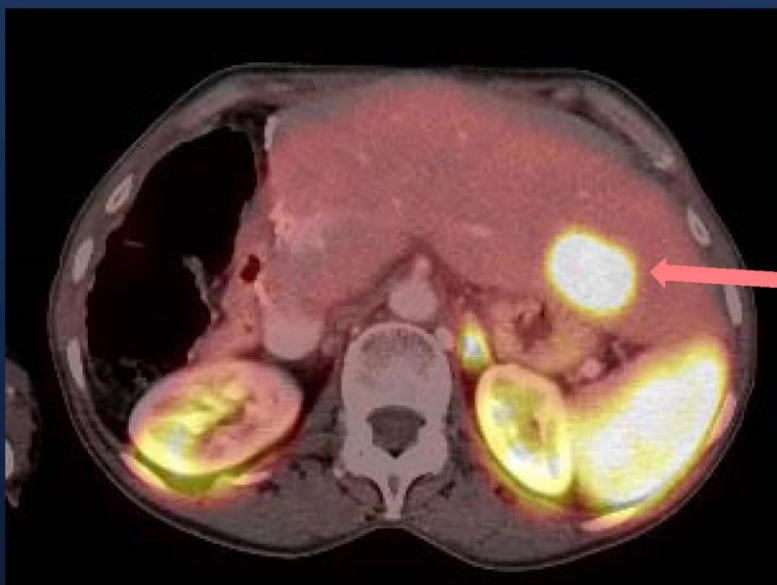
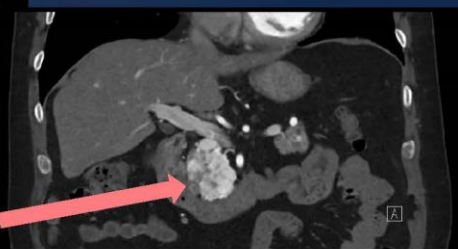
T2-weighted MRI
Axial plane
Pancreatic cysts
Possible cystadenoma



Contrast-enhanced MRI
Axial plane
Pancreatic cysts
Possible cystadenoma



Contrast-enhanced CT
Axial and coronal planes
Pancreatic neuroendocrine
tumor (PNET)



PET/CT with Ga68-dotatate
("NetSpot")
Metastatic PNET

Tumors associated with VHL

Epididymal cystadenoma

- Tumor in scrotum adjacent to testicle
- 25-60% of male VHL patients
- Palpable lump
- Benign, usually not treated



Ultrasound image
from
<http://www.radiopaedia.com>
Epididymal cystadenoma

Is CT Harmful?

- CT involves x-rays, which are ionizing radiation
- Ionizing radiation in large doses is known to cause cancer
- Ionizing radiation in low doses has unknown effects
- Risk of radiation should be considered in patients who are **young** and receive **multiple scans**

Is MRI Harmful?

- Magnetic fields used in MRI have no known health effects
- In 1990s, Gadolinium contrast agents had potential to cause Nephrogenic Systemic Sclerosis in patients with renal failure
- Recently, persistence of gadolinium in bone, skin, and parts of the brain has been shown in patients with normal renal function

Nephrogenic Systemic Sclerosis (NSF)

- First cases reported in 2000
- Linked to MRI contrast material in 2006
- Newer contrast agents used since 2008 → no new cases of NSF
- Recent meta-analysis of 17 studies shows no cases of NSF with newer MRI contrast agents.
 - Woolen SA, Shankar PR, Gagnier JJ, MacEachern MP, Singer L, Davenport MS. Risk of Nephrogenic Systemic Fibrosis in Patients With Stage 4 or 5 Chronic Kidney Disease Receiving a Group II Gadolinium-Based Contrast Agent: A Systematic Review and Meta-analysis. JAMA internal medicine 2020;180(2):223-230.

Nephrogenic Systemic Sclerosis (NSF)

According to FDA, as of December 2009:

- Omniscan – 13 million doses, 382 cases
- Magnevist – 23 million doses, 195 cases
- MultiHance – 10.5 million doses*, 0 cases
- ProHance – 14.5 million doses*, 0 cases

*as of 6/2012 according to Bracco website

NSF was never observed in patients with normal kidney function.

“Gadolinium Deposition Disease”

- Traces of gadolinium have been detected in bone, skin, and parts of the brain in patients who have had contrast-enhanced MRI
- Modern contrast agents are very weakly associated with this deposition
- No known clinical abnormality is associated with these deposits



Patient Self-Advocacy

- Always good to know as much as you can about the disease and imaging and treatment issues
- Patients do not usually benefit from “managing” their own care e.g. insisting on ultrasound instead of CT or MRI
- My opinion: academic medical centers have fewer conflicts of interest in the choice of imaging and therapies

Summary

- Imaging plays a central role in the management of Von Hippel-Lindau Disease
- Increasing life expectancy of VHL patients is attributed to better imaging and clinical surveillance
- Early detection of VHL-associated tumors allows more effective intervention

2020 Annual VHL Family Meeting
October 24, 2020

Screening Guidelines

Othon Iliopoulos, MD, PhD



E. Von Hippel

<https://www.vhl.org/wp-content/uploads/2019/11/Active-Surveillance-Guidelines.pdf>

Guidelines for surveillance of VHL patients



Arvin Lindau

Othon Iliopoulos, MD, PhD

Associate Professor of Medicine
Massachusetts General Hospital Cancer Center
Harvard Medical School
Director, MGH VHL/Hereditary Kidney Cancer Program
Director, MGH HEMANGIOBLASTOMA CENTER



Why should we do surveillance

Prevent mortality AND morbidity from the disease

Identify and treat Renal Cell Cancers (RCC) less than 3 cm

Differentiate between adrenal adenomas and pheochromocytomas

Diagnose and treat occult Paragangliomas (PGs)

Diagnose and treat early pancreatic neuroendocrine tumors (pNET) and prevent their metastasis

Diagnose, follow and time the intervention for CNS Hemangioblastomas (HB)

Diagnose extra lymphatic sac tumors (ELST)



What determines when to start (initiation)
and how often to perform surveillance (frequency)

INITIATION is based on the earliest age of onset of the VHL-associated lesion

FREQUENCY determined on the
growth rate
location
metastatic potential
? mutation

How early can VHL lesions be detected

	Age at diagnosis	Most common ages at diagnosis
CNS		
Retinal hemangioblastomas	0-68 years	12-25 years
Endolymphatic sac tumors	1-50 years	16-28 years
Cerebellar hemangioblastomas	9-78 years	18-25 years
Brainstem hemangioblastomas	12-46 years	24-35 years
Spinal cord hemangioblastomas	12-66 years	24-35 years
Viscera		
Renal cell carcinoma or cysts	16-67 years	25-50 years
Pheochromocytomas	4-58 years	12-25 years
Pancreatic tumor or cyst	5-70 years	24-35 years
Epididymal cystadenomas	17-43 years	14-40 years
APMO or broad ligament cystadenoma	16-46 years	16-46 years

How early can VHL lesions be detected

	Age at diagnosis	Most common ages at diagnosis
CNS		
Retinal hemangioblastomas	0-68 years	12-25 years
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Pancreatic tumor or cyst	5-70 years	24-35 years
Epididymal cystadenomas	17-43 years	14-40 years
APMO or broad ligament cystadenoma	16-46 years	16-46 years

Newborns, Infants and Children

At Birth:

Pediatrician to look for signs of neurological disturbance
(nystagmus, strabismus, white pupil, other)

Routine newborn hearing surveillance.

N. Ehler & O. A. Jensen

Juxtapapillary Retinal Hemangioblastoma (Angiomatosis Retinae) in an Infant: Light Microscopical and Ultrastructural Examination

Ultrastructural Pathology. 1982, 3(4):pp 325-333

Age 1-4:

Annual physical exam (blood pressure, vision, or hearing symptoms).

Annual retinal examination by an ophthalmologist skilled in diagnosis and management of retinal disease

Annual neurological exam (nystagmus, strabismus, white pupil, vision)

Ages 5-10:

Annually

Annual physical exam including detailed neurological exam (includes hearing exam)

Annual retinal examination (eye dilation)

Annual test for pheochromocytoma

Blood or 24 hour urine catecholamines

Epinephrine, nor-epinephrine, fractionated metanephrines and nor-metanephrines

Abdominal MRI or MIBG scan only if biochemical abnormalities found

Abdominal ultrasonography annually from 8 years or earlier if indicated



Ages 5-10 (continued)

Every 2-3 Years

Audiology assessment by an audiologist

Annually if any hearing loss, tinnitus, or vertigo is found

In the case of repeated ear infections, MRI with contrast of the internal auditory canal using thin slices, to check for a possible ELST.



Ages 10-14:

Annual physical exam (including detailed neurological exam and hearing)

Annual retinal examination

Annual test for pheochromocytoma

MRI of the brain and spine every 1-2 years



Ages 14 or 15+:

Annual physical exam (including detailed neurological exam and hearing)

Annual retinal examination

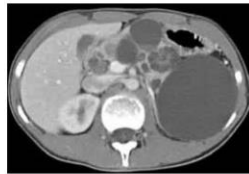
Annual test for pheochromocytoma

MRI of the brain and spine every 1-2 years

MRI of the abdomen (kidneys, adrenals, pancreas) every 1-2 years



RCC less than 3 cm



The 3 cm rule applies to "Solid RCC"

What is the permissive size of a CYST?



Safety of Gadolinium based MRI contrast agents

Nephrogenic Systemic Fibrosis

GFR < 30cc/min

Tissue deposition ?

NOT with macrocyclic gadolinium

Brand name	Generic name	Chemical Structure
Dotarem†	gadoterate meglumine	Macrocyclic
Eovist	gadoxetate disodium	Linear
Gadavist†	gadobutrol	Macrocyclic
Magnevist	gadopentetate dimeglumine	Linear
MultiHance	gadobenate dimeglumine	Linear
Omniscan‡	gadodiamide	Linear
OptiMARK‡	gadoversetamide	Linear
ProHance†	gadoteridol	Macrocyclic

J. Ramalho, R.C. Semelka, M. Ramalho, R.H. Nunes, M. AlObaidy and M. Castillo
Gadolinium-Based Contrast Agent Accumulation and Toxicity: An Update
 American Journal of Neuroradiology 2016, 37 (7): 1192-1198

Do all VHL patients need surveillance for pheo/PG ?

GENOTYPE - PHENOTYPE CORRELATIONS

Classification	Phenotype	Germ-line mutations
Type I	H + RCC	46% Deletions 10% Nonsense 44% Missense N78H/S/T L184P/R S111R S80R/I
Type II		96% Missense
IIA	PHEO+ H + RCC (low)	Y98H Y112H
IIB	PHEO+ H + RCC (high)	V74G R161G R167W/Q/G L178P/Q/V
IIC	PHEO only	L188V G114S F119S V84L V166F S68W

Penetrance is almost 100%

Expressivity widely variable

VHL and pregnancy - 1

Small cohort of patients comparing pregnant VHL pt to match age controls

Prospective studies of pregnant VHL women without comparison group

Conflicting data

Evidence indicates there is NO acceleration of tumor growth

VHL and pregnancy - 2

MRI with NO contrast poses no problem to fetus or mother at any trimester

Gadolinium use in the FIRST trimester may increase risks to newborn
(skin lesions, inflammatory or rheumatic conditions)

Kanal E, Barkovich AJ, Bell C, Borgstede JP, Bradley WG Jr, Froelich JW, et al.
ACR guidance document on MR safe practices: 2013. Expert Panel on MR
Safety. *J Magn Reson Imaging* 2013;37:501–30.

Less than 0.04% gadolinium is excreted in milk only within the 24 hours

Theoretically breastfeeding should not be interrupted

Out of abundance of caution we could suggest milk banking before MRI
and resume lactation 48 hours after MRI

Committee Opinion No. 723: Guidelines for Diagnostic Imaging During Pregnancy
and Lactation. *Obstet Gynecol.* 2017;130:e210-e216. [PubMed: 28937575]



Thank you.....



.....Time for questions



VHLA Suggested Active Surveillance Guidelines

Until a cure is found, surveillance is a patient's strongest defense to prevent severe VHL complications.

[*\[Revised 4/24/2020\]*](#)

Surveillance is the testing of individuals at risk for von Hippel-Lindau disease (VHL) who do not yet have symptoms, or who are known to have VHL but do not yet have symptoms in a particular area. The unaffected organs should still be screened.

Modifications of surveillance schedules may sometimes be done by physicians familiar with individual patients and with their family history. Once a person has a known manifestation of VHL, or develops a symptom, the follow-up plan should be determined with the medical team. More frequent testing may be needed to track the growth of known lesions.

People who have had a DNA test and do not carry the altered VHL gene may be excused from testing.

In order to monitor the most critical areas of the brain and spinal cord in the most efficient and cost-effective manner, CNS MRIs should include the brain, cervical, thoracic, and lumbar spine. Scans should be ordered as no less than a 1.5T MRI with and without contrast, with thin cuts through the posterior fossa, and attention to inner ear/petrous temporal bone to rule out both ELST and hemangioblastomas of the neuraxis.

Surveillance Modality (Tumors being screened)	AGE ¹						Pregnancy ¹¹
	<5 years	Beginning at age 5y	Beginning at age 11y	Beginning at age 15y	Beginning at age 30y	Beginning at age 65y ¹	
History and Physical Examination²	Yearly from age 1 year	Yearly	Yearly	Yearly	Yearly	Yearly	Prior to conception ¹¹
Blood Pressure and Pulse (Pheochromocytomas/paragangliomas)	Yearly from age 2 years	Yearly	Yearly	Yearly	Yearly	Yearly	Prior to conception ¹¹
Dilated Eye Examination³ (Retinal Hemangioblastomas)	Every 6-12 months, beginning before age 1 year	Every 6-12 months	Every 6-12 months	Every 6-12 months	Yearly	Yearly	Prior to conception, then Every 6-12 months ¹¹
Metanephrines⁴ (Pheochromocytomas/paragangliomas)	—	Yearly	Yearly	Yearly	Yearly	Stop routine ¹	Prior to conception ¹¹
MRI Brain and Spine w/wo Contrast^{5,6,7} (CNS Hemangioblastomas)	—	—	Every 2 years ⁸	Every 2 years ⁸	Every 2 years ⁸	Stop routine ¹	Prior to conception ¹¹
Audiogram (Endolymphatic sac tumors)	—	—	Every 2 years	Every 2 years	Every 2 years	Stop routine ¹	—
MRI Abdomen w/wo Contrast^{5,6,7} (Renal cell carcinomas, Pheochromocytomas/paragangliomas, Pancreatic neuroendocrine tumors/cysts)	—	—	—	Every 2 years ⁹	Every 2 years ⁹	Stop routine ¹	Prior to conception ¹¹
MRI Internal Auditory Canal¹⁰ (Endolymphatic sac tumors)	—	—	—	Once	—	—	No specific changes

Notes:

Your clinician may suggest more frequent surveillance based on existing lesions. In such a circumstance, it is important to be seen by a VHL specialist.

- 1 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, this applies to all other routine screening/surveillance tests in asymptomatic patients. However, patients presenting with signs/symptoms should be evaluated with appropriate testing/imaging regardless of age.
- 2 Age-appropriate history and physical examination to include: Neurologic examination, auditory and vestibuloneural questions and testing, visual symptoms, catecholamine excess symptom assessment (headaches, palpitations, diaphoresis, hyperactivity, anxiety, polyuria, abdominal pain).
- 3 Dilated, in-person eye examination including ophthalmoscopy to occur every 6-12 months based on quality of examination obtained (especially in a child) and perceived adherence to follow-up. Consider examination under anesthesia in young children in whom a detailed eye examination cannot be adequately obtained in the clinic. Consider including ultrawidefield photography and ultrawidefield fluorescein angiography, but these should not replace a dilated eye examination with a specialist with experience in retinal manifestations of VHL.
- 4 Plasma free metanephrines (preferred, due to its higher sensitivity) or fractionated 24-hour urinary free metanephrines.
- 5 Use macrocyclic/class II gadolinium-based contrast agents. MRI of the neuroaxis may be obtained at the same time as MRI abdomen, and may be performed under a single long anesthesia event, especially in children. However, both 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, nor is it recommended to evaluate the abdominal organs solely using a neuroaxis protocol. See footnote #6 and #7 for how to combine these protocols.
- 6 Based on contraindications (metallic implants, renal failure, etc.), the following order of imaging priority applies: MRI (with and without contrast) > MRI (without contrast) > CT (with contrast) > CT (without contrast) > US (kidneys, adrenals and pancreas only) > Endoscopic US (pancreas only). See also footnote #5 and #7.
- 7 Timing of contrast administration when imaging multiple organ systems together should be as follows: Obtain non-contrasted images of CNS and abdomen first, then give contrast using a power injector and perform multi-phase contrast-enhanced imaging of the abdomen including pancreas and kidneys during the late arterial phase and delayed venous phases. Then late post-contrast imaging of neuroaxis. See also footnote #5 and #6.
- 8 If no CNS hemangioblastomas, continue routine surveillance every 2 years. If hemangioblastomas are present and there is an increase in hemangioblastoma size, or if the patient has associated symptoms, scans should be yearly (or more frequently), as appropriate (or referred to neurosurgery).**
- 9 If no renal lesions present on initial scan, continue routine surveillance every 2 years. If small tumors (< 3 cm) found, reimaging initially with MRI every 3-6 months to determine stability. Once stability has been determined over 3 consecutive scans, consider extending to every 2 years. If renal mass is > 3 cm, consider a referral to a urologist (preferably familiar with the care of VHL).**
- 10 High-resolution (1mm slice thickness) magnetic resonance imaging of the internal auditory canal. This baseline MRI of the internal auditory canal should be obtained after age 15 years (once the temporal bones have matured), and it should be added onto the MRI of the neuroaxis conducted between ages 15-20 years.
- 11 "Prior" indicates that this surveillance testing should ideally be performed prior to any planned conception, if possible. MRIs performed during pregnancy should be without contrast.

2020 Annual VHL Family Meeting

October 24, 2020

Screening Adherence in Adolescents and Emerging Adults

Samantha Greenberg, MS, CGG

Screening adherence in adolescents and young adults

Samantha Greenberg, MS, MPH, CGC
Huntsman Cancer Institute



How do we keep track and stay on top of screening?

How do we empower?

Surveillance Modality (Tumors being screened)	AGE ¹						Pregnancy ¹¹
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Audiogram (Endolymphatic sac tumors)	—	—	Every 2 years	Every 2 years	Every 2 years	Stop routine ¹	—
MRI Abdomen w/wo Contrast^{5,6,7} (Renal cell carcinomas, Pheochromocytomas/paragangliomas, Pancreatic neuroendocrine tumors/cysts)	—	—	—	Every 2 years ⁹	Every 2 years ⁹	Stop routine ¹	Prior to conception ¹¹
MRI Internal Auditory Canal¹⁰ (Endolymphatic sac tumors)	—	—	—	Once	—	—	No specific changes

Overview

- ▶ Screening: Why can it be challenging to stay on top of scans?
- ▶ Kids, adolescents and young adults: What's going on in their life?
- ▶ When is it 'right' to transition VHL care to the young adult, instead of the parent?
- ▶ How can we encourage this transition?
- ▶ Who can help with managing VHL care and helping younger VHL patients start to own their management? (hint: everyone!)

What makes screening hard to:

- Remember?
- Follow up on?
- etc?

Please put your answers in the chat—this can be done to everyone or privately

How are these challenges different for your children?

Common challenges related to screening

- Fitting screening(s) into busy lives
- Managing the demands of obtaining multiple screenings, on different timetables
 - Forgetting to schedule screenings for one family member if they're not at the same time as other family
- Stress related to obtaining financial coverage for screenings
- Managing anxiety related to anticipated/actual screening outcomes
 - Anticipatory anxiety peaks around the time of screening
- Ongoing uncertainty and worry if screening results are unclear or require further work-up
- Explaining purpose of screenings to minor children

Slide adapted from Dr. Yelena Wu

What is happening for younger patients with VHL?

	Begin brain/spine MRIs	Begin abdominal MRIs	Begin to manage care
Main aspects	Early adolescence or pre-adolescence (10 to 14 years of age)	Adolescence media (15 to 17 years of age)	Late adolescence (18 even 21 years of age)
Independence	Lack of interest in the activity of the family Changes in mood	Family conflicts Testing of the family values	Acceptance of responsibilities Acceptance of tips
Corporal figure	Importance of the appearance. Fashion	Concern for the physical aspect Training and group membership	Acceptance of their figure Expansion of their groups
Adoption of new styles	Friends of the same gender	Values of the friends. Appointments with suitors	Use of their time. Vocation
Identity	Cognitive Thinking Fantasy. Search for privacy	Intellectual ability Feelings share	Realistic Commitments Acceptance of moral and religious values and sexual.

Source: Gorab, R. (2011). Introducción a la adolescencia en G. R. Fernández PF, Adolescencia y Medicina (595 pp). México, D.F.: Prado-UNAM.

Emerging adulthood (18-25yrs)

- ▶ Typically begins after high school (Arnett)
- ▶ People usually experience:
 - ▶ Instability
 - ▶ Moving job
 - ▶ Identity exploration
 - ▶ Deciding who you are
 - ▶ Self-focused
 - ▶ After leaving routine of home, and before marriage/children/career
 - ▶ Feeling 'in-between'
 - ▶ Beginning to take responsibility for self, but not feeling 'adult'
 - ▶ World of possibilities
 - ▶ Optimism for future, both professionally, personally, and romantically

Big time of transition—both in personal lives and in VHL management!

When do we start the transition from child to adult in terms of VHL care?

- ▶ Technically, when someone turns 18, they are an adult—but is that the right time?
 - ▶ The transition process is not just a split second, but a multi-year process!
 - ▶ Families make individual decisions on the right time to begin
 - ▶ Can be as early as the start of teenage years
- ▶ Many aspects of screening to think about transitioning:
 - ▶ Scheduling
 - ▶ Routine visits
 - ▶ New specialists
 - ▶ Doctor's visits—who answers the questions?
 - ▶ Discussing results from MRIs
 - ▶ Keeping track of what's due for screening
- ▶ Note: Management for some tumors (i.e. pheochromocytomas) can begin with adult specialists as early as puberty

These may start at different times!

What are all of the tasks that get transitioned from parent -> child?

- ▶ Making appointments for screenings
 - ▶ Attending screenings
 - ▶ Keeping a list of past screening dates
 - ▶ Identifying when next screenings are 'due'
 - ▶ Contacting insurance
 - ▶ Identifying symptoms and/or documenting them to contact doctor or for next visit
 - ▶ Describing VHL and implications to others
 - ▶ What else?
-
- ▶ Talk through who is doing what, and what kind of system works for you
 - ▶ "I do, we do, you do" strategy

An example: What might this look like?

Adolescent joins result discussions

Adolescent and parent work to develop ways to 'keep track' of screening

Surveillance Modality (Tumors being screened)	<5 years	AGE ¹					Pregnancy ¹
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Blood Pressure and Pulse (Pheochromocytomas/paragangliomas)	Yearly from age 2 years ¹	Yearly	Yearly	Yearly	Yearly	Yearly	Prior to conception ¹¹
Dilated Eye Examination ¹ (Retinal hemangioblastomas)	Every 6-12 months, baseline	Every 6-12	Every 6-12	Every 6-12	Yearly	Yearly	Prior to conception, then Every 6-12 months ¹¹
Metanephroses ¹ (Pheochromocytomas/paragangliomas)	---	---	---	Every 6 years ⁸	Every 6 years ⁸	Every 6 years ⁸	Prior to conception ¹¹
MRI Brain and Spine w/wo Contrast ^{1,2} (CNS Hemangioblastomas)	---	---	---	---	---	---	Prior to conception ¹¹
Audiogram (Endolymphatic sac tumors)	---	---	---	---	---	---	---
MRI Abdomen w/wo Contrast ^{1,3} (Renal cell carcinomas, Pheochromocytomas/paragangliomas, Pancreatic neuroendocrine tumors/cysts)	---	---	---	Every 6 years ⁸	Every 6 years ⁸	Every 6 years ⁸	Prior to conception ¹¹
MRI Internal Auditory Canal ^{1,4} (Endolymphatic sac tumors)	---	---	---	Once	---	---	No specific changes

IMPORTANT: This is a partnership!

Age 13-18: Adolescent answers doctor's questions first, then parents add on information

Age 18: Adolescent and parent discuss scheduling, and either sign ROI or adolescent takes over management

Age 18-25: Full transition to emerging adult managing care

How can we make this transition (and screening in general) easier?

- Identify barriers to screening adherence
 - What is hardest for the adolescent (and/or you)?
 - Share that with each other
 - And even your care team!
- Think about what is doable or manageable
 - What would be the most efficient schedule for screenings (e.g., during the summer for children)?
 - Is it best to attach screenings to an event (birthday, holiday, etc)?
- Prompts and reminders
 - As they are learning, how can parents help to remind them?
 - Give TIME for them to do it, balancing gentle nudges that teach instead of 'do'
- Talk with your VHL team: Are there resources to help track screening? How can you and/or your family utilize those?

Slide adapted from Dr. Yelena Wu

A photograph of a person skateboarding, with the quote overlaid. The person is in motion, wearing a dark shirt and shorts, with a crowd visible in the background.

It is better to do something than
to do nothing while waiting to do
everything.

~ Winston Churchill

WISEFAMOUSQUOTES.COM

What are other topics that may come up when it comes to screening?

- ▶ **Blood draws:** Concerns re: exposing children to “pokes” (needles)
 - ▶ How have you and/or your child coped with needles and procedures in the past
 - ▶ Is there a favorite item that can come to the scans?
 - ▶ It's okay for you to worry more than them 😊
 - ▶ Over time we can build memories and perceptions that younger family members may not have
 - ▶ Maintain positivity and follow the child's lead!
- ▶ **Adult screenings and adolescent screenings are different!**
 - ▶ The settings are geared towards younger patients
 - ▶ Is there a favorite movie to watch during MRI?
 - ▶ Child life specialists play a crucial role (more to come)

Slide adapted from Dr. Yelena Wu

What else can we do to make screening less challenging? Child Life Specialists!

Child life specialists work with the child's treatment team to meet unique **emotional, developmental and cultural needs** of each child and family by:

- Easing child's fear and anxiety
- Encouraging child's cooperation
- Helping child understand medical procedure
- Facilitating non-medicinal pain management
- Fostering a supportive environment

Slide adapted from Dr. Yelena Wu



Strategies for explaining screening to children

- ▶ Explain the purpose of the scan in developmentally-appropriate terms
 - ▶ "Taking pictures of their bodies"
 - ▶ Showing them family member's scans during clinic visit (images of brain, hands, etc.)
- ▶ Preparing children for the scan
 - ▶ App: Simply Sayin (by Phoenix Children's Hospital)
 - ▶ <https://www.chop.edu/video/getting-mri-cartoon-kids>
 - ▶ <https://www.youtube.com/watch?v=u0sf-Y8SkAq>
 - ▶ Kids Health printouts: <https://kidshealth.org/en/parents/mri.html>



Getting an MRI: A Cartoon for Kids



Emerging research: How can we help patients with VHL stay on top of screening, especially during their transition?



- Are there external factors that influence screen adherence among individuals with rare hereditary cancer syndromes?



- If so, what types of factors are those?
 - Demographic
 - Interpersonal
 - Co-occurring
 - Screening/Procedures



- How do changes in age affect adherence? (if at all)

Amy Whitburn
Genetic Counselor



How was this studied?



- Patients were identified through: the Family Cancer Assessment Clinic at Huntsman Cancer Institute
- Criteria:
 - Age 10-39 at some point from 1/1/2010-12/31/2018
 - Genetic diagnosis of VHL prior to an *event that would change screening recommendations*
 - Tumor diagnosis, surgery, etc.

Slide courtesy of Amy Whitburn

Factors looked at in the electronic medical records



Demographic:
Gender
Age/Age grouping
Address Zone
Employed/Student
Years of Education
Primary Language
Ethnicity
Race



Interpersonal:
Marital Status
of Children
Appointment Companion
Affected Sibling
Affected Child
Affected Parent
Affected "Other"



Co-Occurring:
Smoking Status
Alcohol Use
Substance Abuse
Mental Health dx.
Other Chronic Health Condition

Slide courtesy of Amy Whitburn

Who are our patients here at Huntsman?

- ▶ We follow over 40 patients with VHL at our Huntsman Cancer Institute CCC
- ▶ 25 (62.5%) of our patients are between the ages of 10-39
 - ▶ 7 did not have previous surgery or tumor diagnosis from 2010-2018 that qualified them for evaluation



Sample Size:
N=7



Average Age:
23.71



Age Grouping:
Adolescence: 1
Emerging Adult: 2
Young Adult: 3



Gender:
Female: 3
Male: 4



Primary Language:
English (7)



Years of Education:
Undocumented (7)



Race:
White or Caucasian (7)

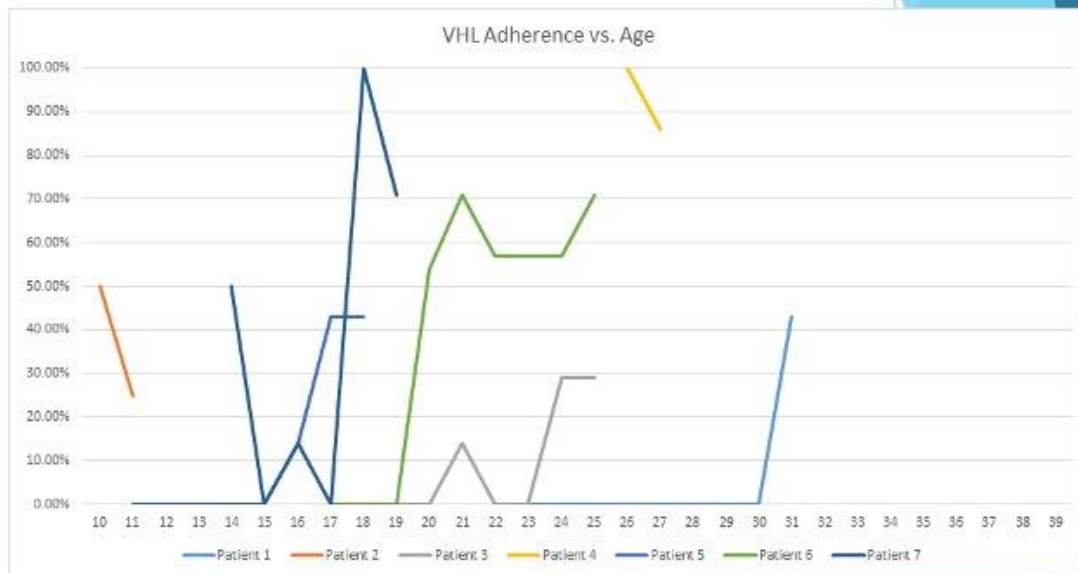


Ethnicity:
Not Hispanic/Latino (7)

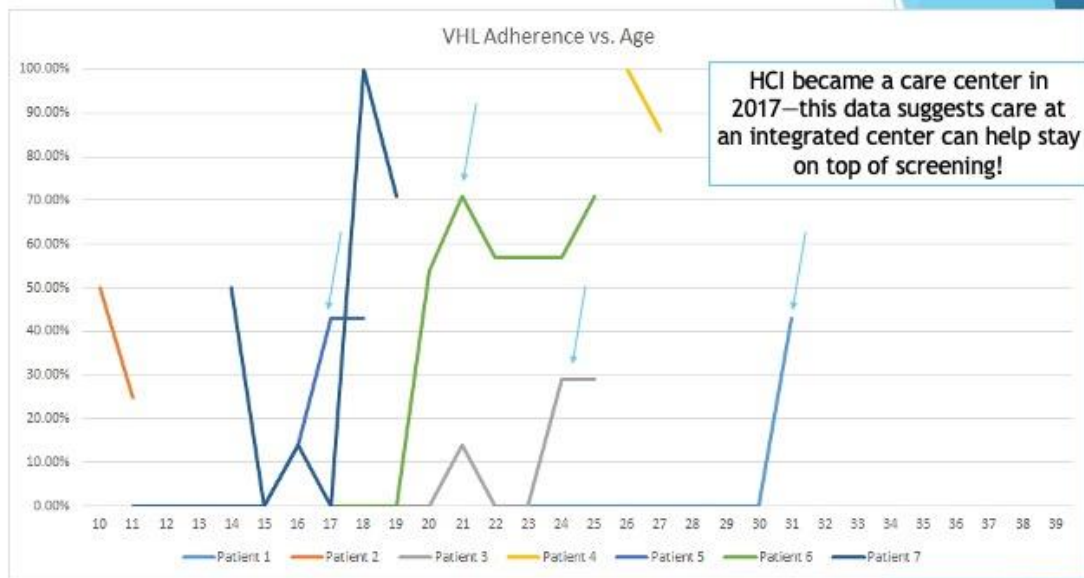
Slide courtesy of Amy Whitburn

How did we measure adherence?

- ▶ Screenings included:
 - ▶ Ophthalmology annually
 - ▶ Metanephrines annually
 - ▶ Audiology every 3 years
 - ▶ Abdominal MRI every 2 years (if >16y)
 - ▶ Brain MRI every 2 years (if >16y)
 - ▶ Spinal MRI every 2 years (if >16y)
 - ▶ (Physical exam annually)
- ▶ Total number of screens within the timeframe/Total number of eligible scans
 - ▶ % adherence



Slide courtesy of Amy Whitburn



Slide courtesy of Amy Whitburn

Some observations on VHL Adherence (n=7)

- ▶ Most people had their first tumor/cancer diagnosis during ages 10-39
- ▶ All of our VHL patients did not have children at the time
 - ▶ Managing only one person's care rather than care for the family
- ▶ Co-occurring conditions such as mental health diagnoses or chronic conditions existed for some patients
 - ▶ Important that we take the whole self into account when thinking about screening
- ▶ Not all things that impact adherence are documented
 - ▶ Other research is needed to understand patient and provider perspectives
- ▶ Having a 'point of contact' is a helpful way to stay on top of what's due and when

Summary

- ▶ People change over time, and how we manage screening needs to change also
- ▶ Transitioning from parent-led screening to child-led screening is a personal decision
- ▶ Open lines of communication to discuss what a transition looks like
- ▶ Utilize tips and tricks that will help keep track of and on top of screening
- ▶ There are LOTS of resources, and VHL Care Centers are here to help!

2020 Annual VHL Family Meeting
October 24, 2020

Research Update

Mei Koh, PhD

Research Update:

The HIFs in Kidney Cancer

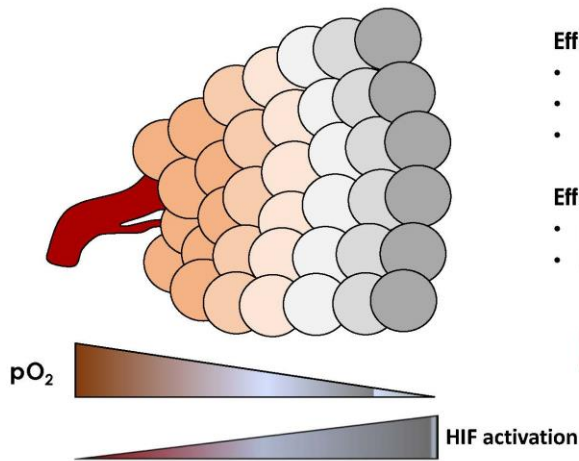
Mei Yee Koh, PhD
Assistant Professor,
Dept of Pharmacology and Toxicology
Investigator, Huntsman Cancer Institute
University of Utah

COI Disclosure: I have equity in Kuda Therapeutics LLC



Low oxygen or hypoxia is a component of all solid tumors

All solids tumors and their metastasis (>100 μ M) experience regions of hypoxia



Effects on tumor cells

- Promotes Chemo/Radioresistance
- Associated with increased genetic instability
- Increases Invasion/metastasis

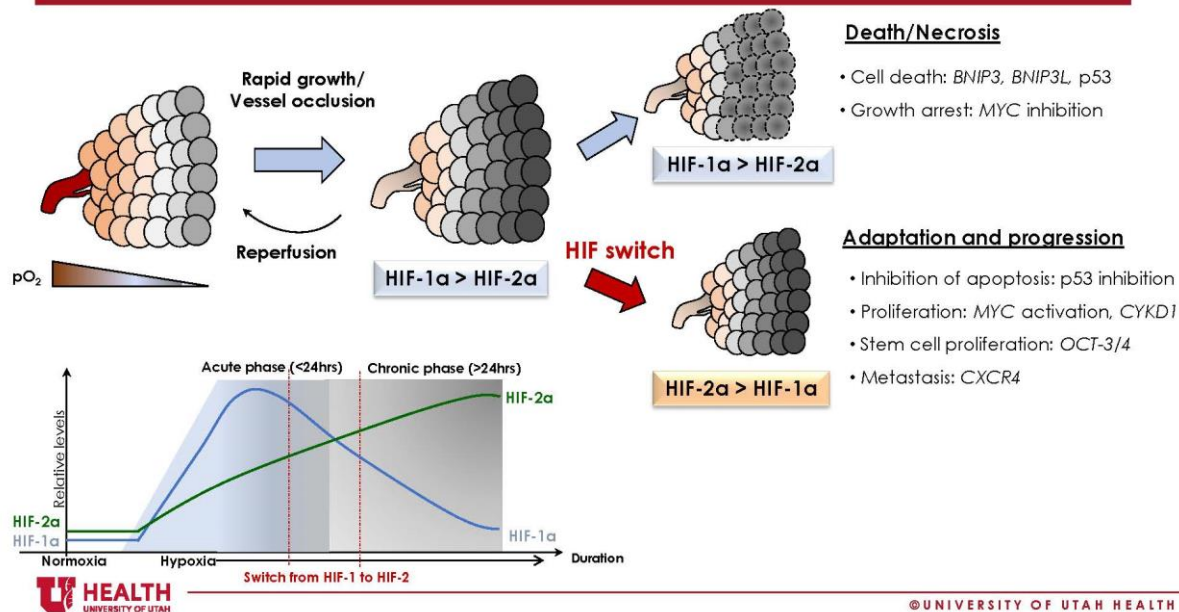
Effects on tumor microenvironment

- Promotes macrophage infiltration
- Suppresses the cytotoxicity of T-cells

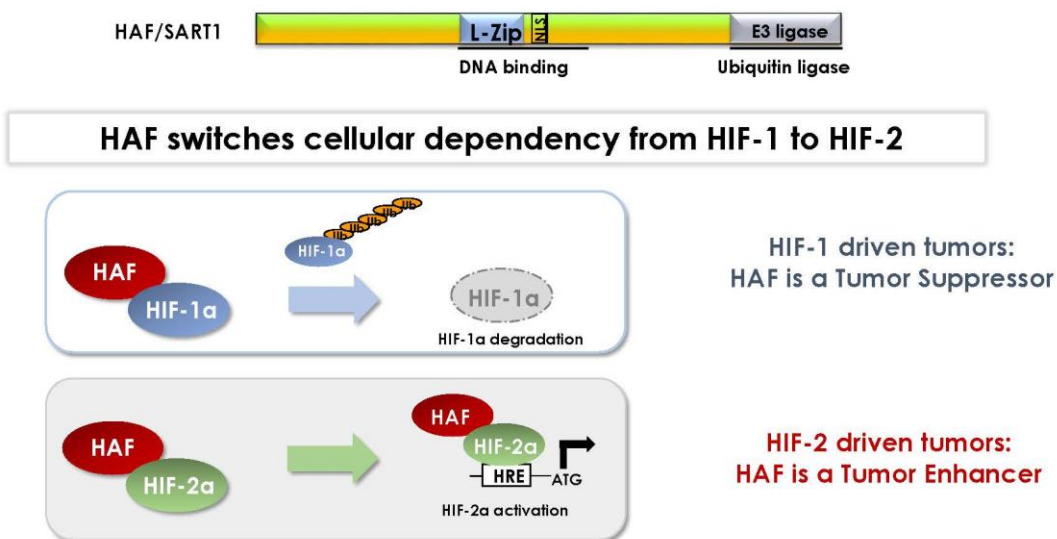
➔

Aggressive disease!

Hypoxia is a Dynamic Component of the Tumor

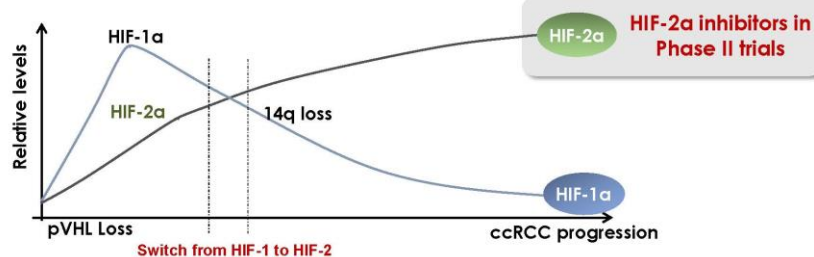


The Hypoxia-associated Factor (HAF) promotes HIF-2 activation



The HIFs play disparate role in ccRCC

pVHL loss in ~90% of ccRCC – phenocopies chronic hypoxia (constitutive HIF)



HIF-1α plays a tumor suppressor role in ccRCC

- HIF-1α overexpression *inhibits* ccRCC growth (Raval, Mol Cell Bio 2005)
- 43% (7/16) homozygous deletion of *HIF1A* in ccRCC cell lines (Shen, Canc Discovery 2011)
- 14q loss (*HIF1A* locus) associated with decreased OS (Monzon, Modern Pathology 2011)

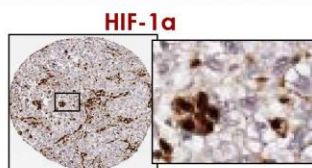
Primarily based on functional studies in cell lines

HIF-2α drives tumor growth and metastasis in ccRCC

- HIF-2α overexpression *promotes* ccRCC growth (Raval, MCB 2005; Kondo, PLOS Bio 2003)
- HIF-2α deletion abrogates *in vivo* ccRCC growth (Kondo PLOS Bio 2003; Koh, Can Res 2015)
- HIF-2-CXCR4 axis associated with ccRCC metastasis (Vanharanta Nat Med 2016)

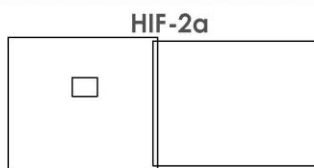
What is the role of HAF in ccRCC progression?

Analysis of HAF and the HIFs in 400 ccRCC patients



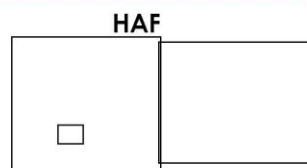
HIF-1α		
Patient Characteristics	Mean	P-value
Clinical T Stage (N = 380)		
T1 (90)	0.028	0.005
T2 (95)	0.040	
T3 (110)	0.020	
T4 (85)	0.055	
Clinical M Stage		
No	0.024	0.02
Yes	0.033	

- HIF-1α increased with tumor stage
- Higher HIF-1α in metastatic tumors



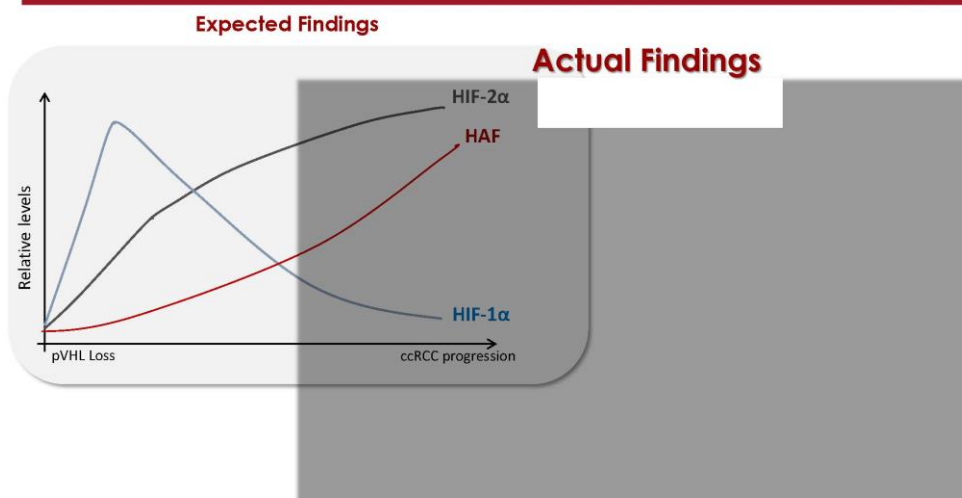
HIF-2A		
Patient Characteristics	Mean	P-value
Clinical T Stage (N = 380)		
T1	0.419	<0.001
T2	0.195	
T3	0.099	
T4	0.166	
Clinical M Stage		
No	0.219	0.01
Yes	0.137	

- HIF-2α/HAF decrease with tumor stage
- Lower HIF-2α/HAF in metastatic tumors



HAF		
Patient Characteristics	Mean	P-value
Clinical T Stage (N = 380)		
T1	0.164	<0.001
T2	0.112	
T3	0.055	
T4	0.012	
Clinical M Stage		
No	0.113	0.001
Yes	0.049	

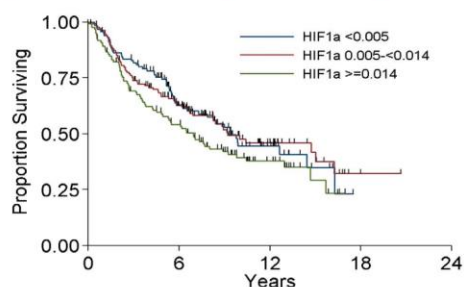
Findings are Contrary to the Expected Findings



HIF-1α is associated with decreased OS in ccRCC

HIF-1α correlates to decreased OS

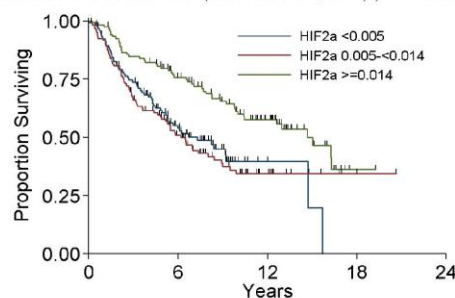
HR per increase in 10% 1.39 (95% CI: 1.06, 1.83) $p = 0.02$



Number at risk	0	6	12	18	24
<0.005	116	55	18	0	0
0.005-<0.014	135	69	21	1	0
>=0.014	120	58	18	0	0

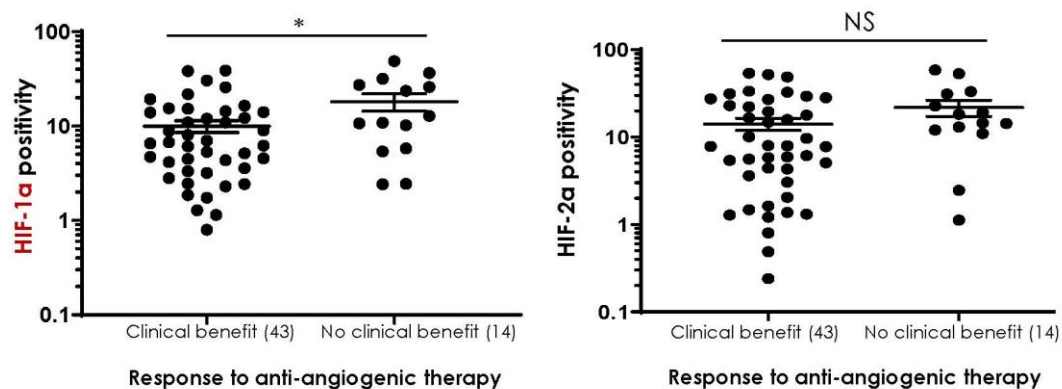
HIF-2α correlates to increased OS

HR per increase in 10% 0.87 (95% CI: 0.80, 0.93) $p = <0.001$



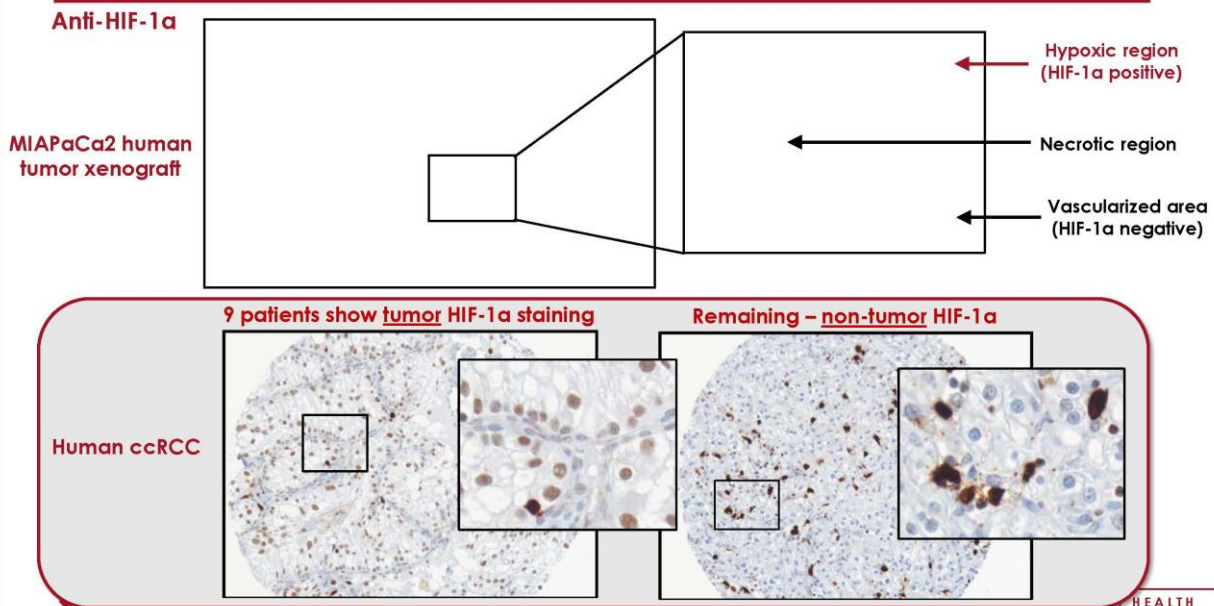
Number at risk	0	6	12	18	24
<0.005	117	46	2	0	0
0.005-<0.014	120	50	12	1	0
>=0.014	119	79	41	1	0

HIF-1a is Associated with Resistance to Anti-angiogenic Therapy

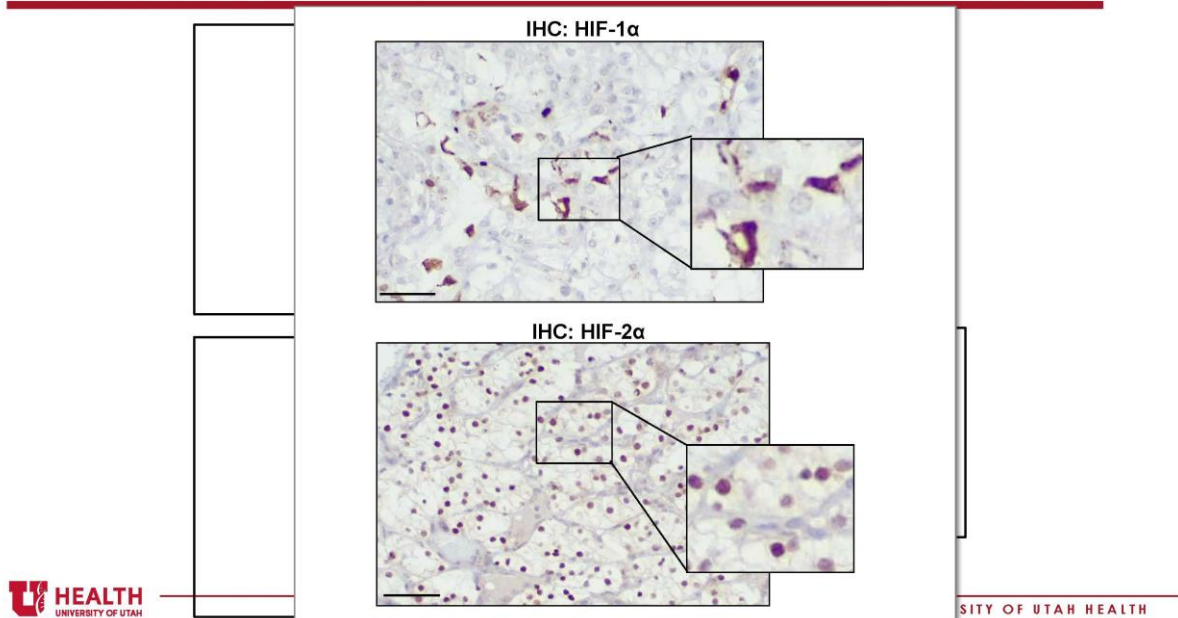


Why is HIF-1a expressed in ccRCC and what is it doing?

HIF-1a staining in ccRCC is not representative of hypoxia

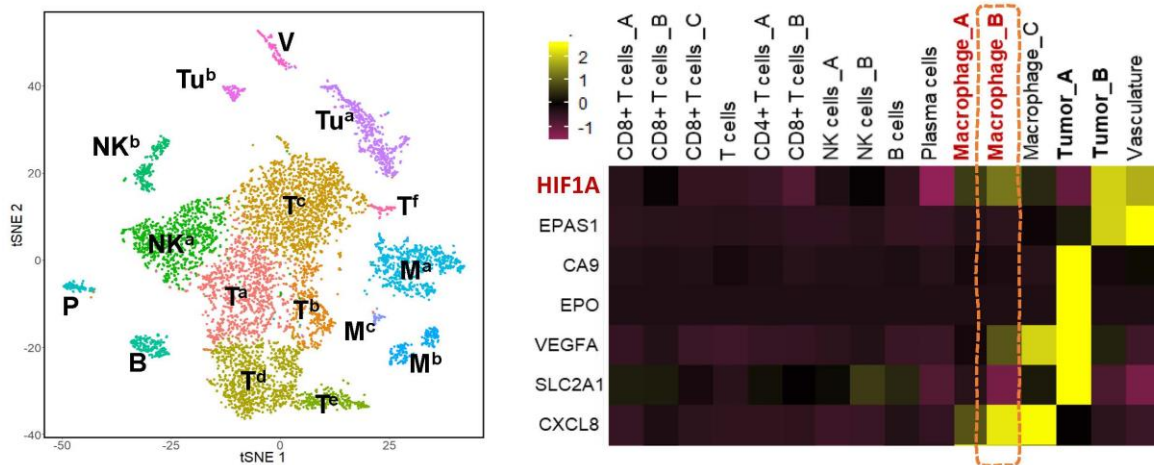


HIF-1α is primarily expressed within non-neoplastic cells

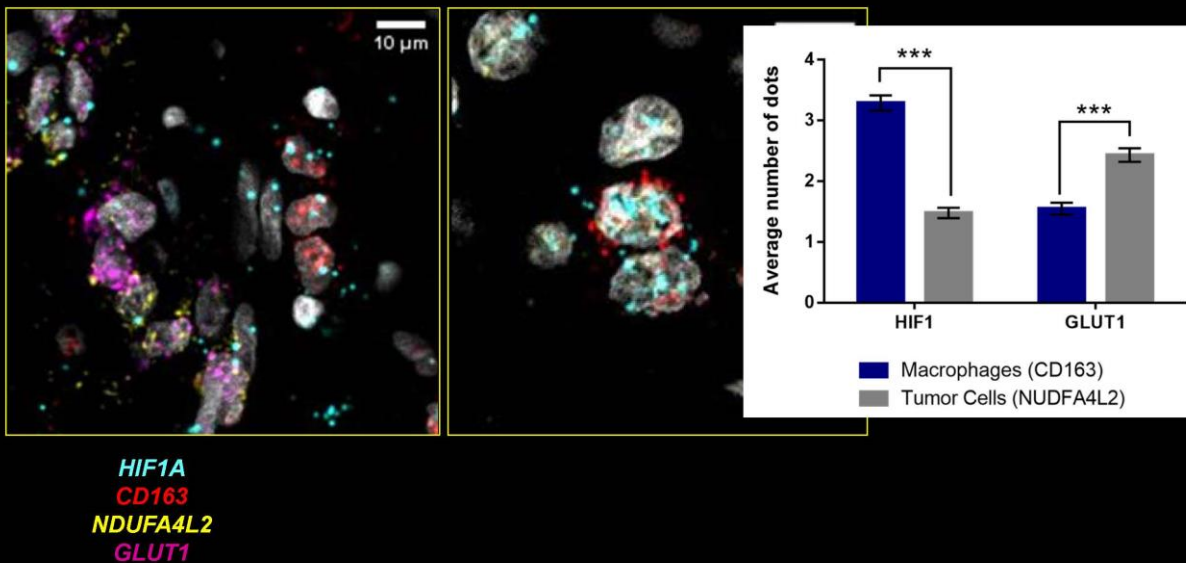


SC Sequencing Identify Macrophages as High *HIF1A* Expressing Cells

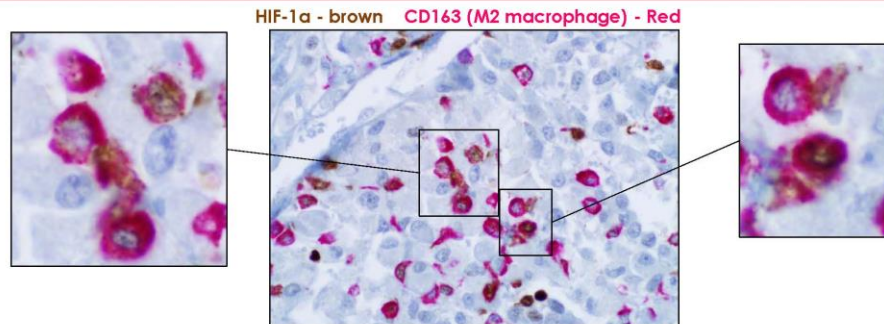
- SCmRNA (10x Genomics) Seq of 3 pats with Grade III/IV ccRCC with paired uninvolved
- Sequence data from 7569 ccRCC cells and 2464 uninvolved cells passed QC (Cell Ranger)



HIF1A is Expressed in CD163+ Macrophages But NOT in ccRCC Cells



HIF-1 α is Primarily Expressed in CD163+ M2 Polarized TAMs

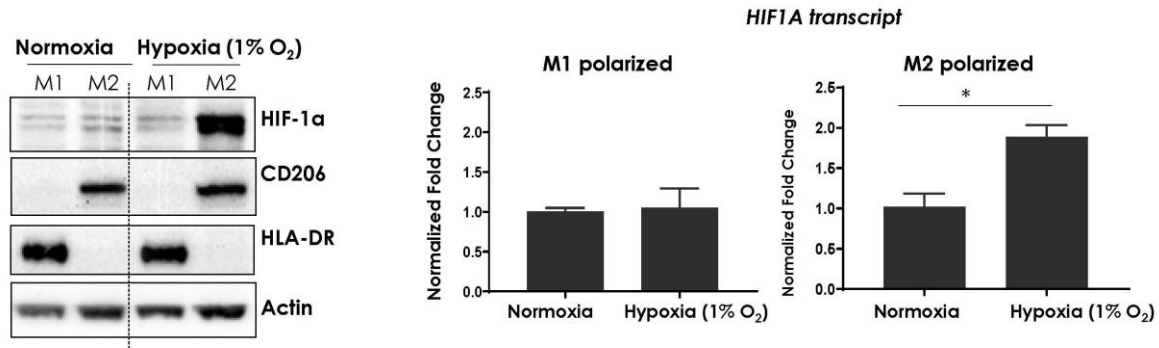


Tumor-associated macrophages (TAMs) – Typically M2 polarized (CD163+)

- Pro-angiogenic, secrete growth factors, MMPs
- Secrete CCL2 (HIF target) – chemoattractant for additional monocytes/macros
- Produce IL-10 (HIF target) – immunosuppressive
- Associated with poor outcome in multiple tumor types

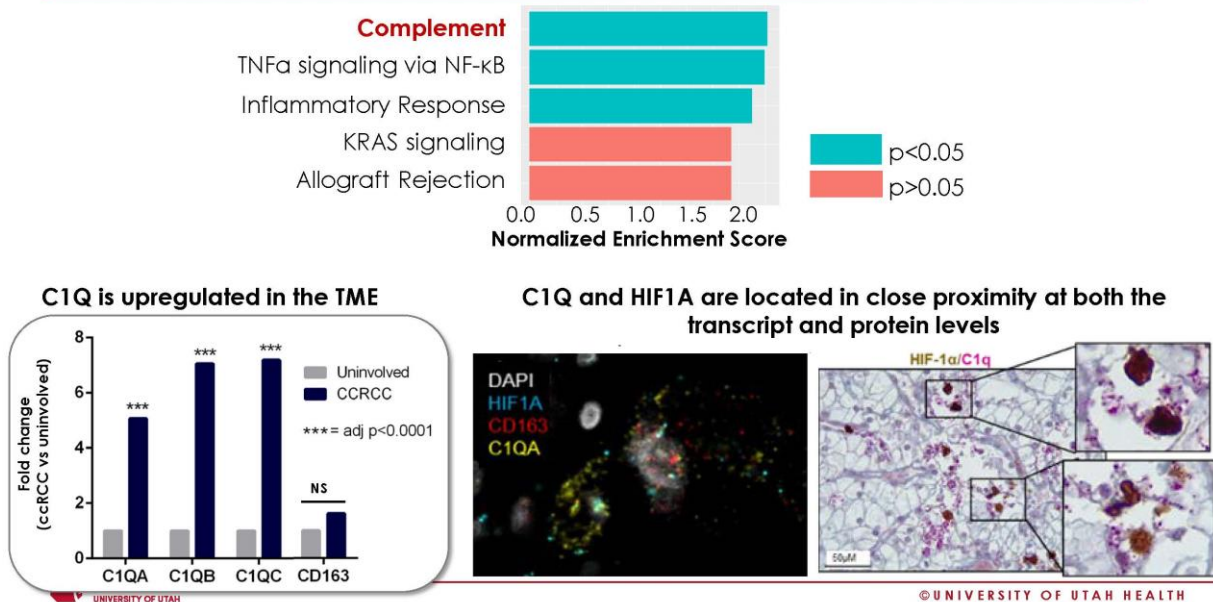
HIF-1 α not expressed in T-cells, B-cells, endothelial cells. V rare in ccRCC tumor cells

HIF-1a is Associated with M2 Polarization in vitro

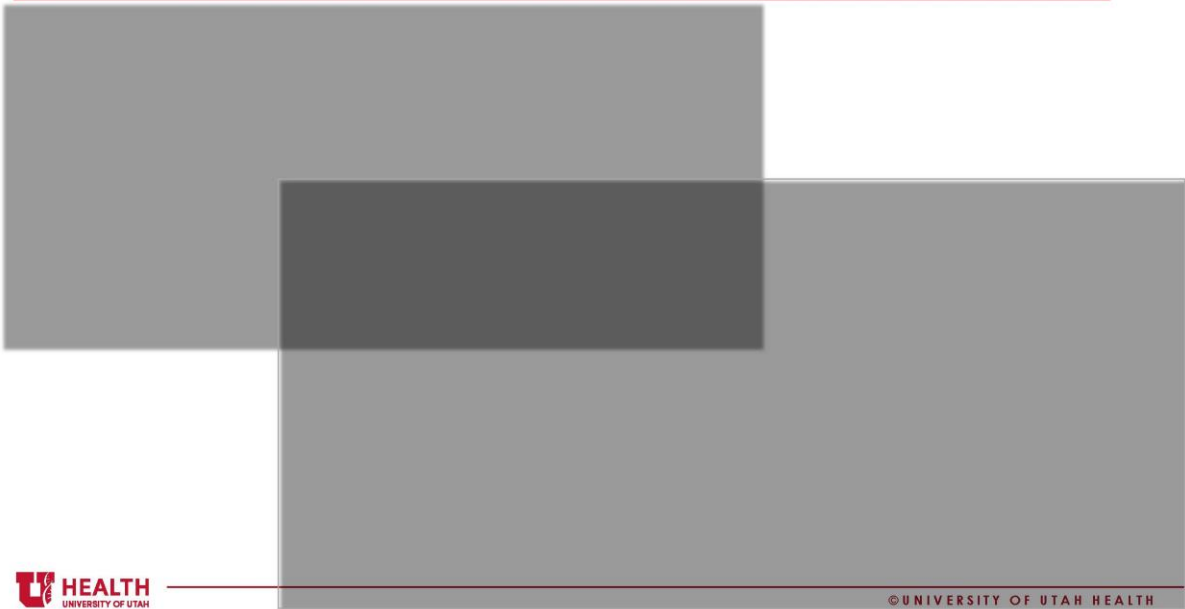


- HIF-1a is transcriptionally activated in TAMs
- In tumor cells, HIF (HIF-2?) is activated post-transcriptionally

HIF-1a is Associated with Complement Pathway Activation



C1Q is associated with decreased PFS and OS in ccRCC



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HIF-1α Deletion Inhibits ccRCC Tumorigenesis in Mice



ARTICLE

<https://doi.org/10.1038/s41467-020-17873-3>

OPEN

HIF-1α and HIF-2α differently regulate tumour development and inflammation of clear cell renal cell carcinoma in mice

Rouven Hoefflin^{1,15}, Sabine Harlander^{2,3,15}, Silvia Schäfer^{1,4,5}, Patrick Metzger^{5,6}, Fengshen Kuo⁷, Désirée Schönenberger^{2,3}, Mojca Adlesic^{1,4}, Asin Peighambari^{1,4,5}, Philipp Seidel^{1,4}, Chia-yi Chen⁸, Miguel Consenza-Contreras⁸, Andreas Jud⁹, Bernd Lahrmann¹⁰, Niels Grabe¹⁰, Danijela Heide¹¹, Franziska M. Uhl^{1,5}, Timothy A. Chan⁷, Justus Duyster^{1,12}, Robert Zeiser^{1,4,12}, Christoph Schell⁸, Mathias Heikenwalder¹¹, Oliver Schilling^{8,12,13}, A. Ari Hakimi^{7,14}, Melanie Boerries^{6,12,13} & Ian J. Frew^{1,2,3,4,5,12}✉

Check for updates



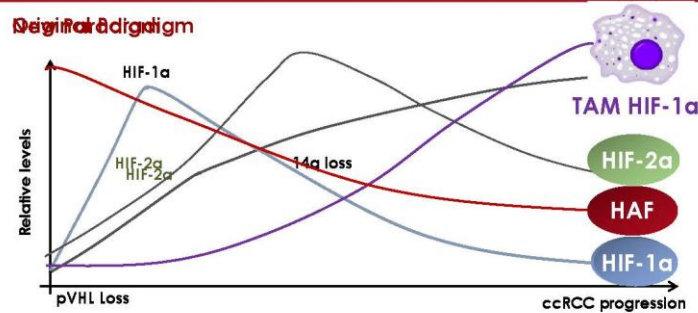
p53, Rb null

VHL, p53, Rb null

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Summary



- ❑ Revised the HIF-1/HIF-2 paradigm for ccRCC: HIF-1α in TAMs may play a pro-tumorigenic role
 - ❑ HIF-1 and HIF-2 both contribute to ccRCC initiation and progression – not a binary pro- and anti-tumor effect as previously proposed
- ❑ We show for the first time the association of HIF-1α with M2 macrophage polarization
- ❑ HIF-1α may be a valid target in ccRCC - contributes to the tumor promoting properties of TAMs
- ❑ Studies are ongoing to characterize the HIF-1α-C1q axis and its contribution to ccRCC progression

Acknowledgements



- Sophie Cowman
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- Benjamin Maughan
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- Ken Boucher (biostatistics)

HCI GU Disease Oriented Team Pilot Award



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- Xiande Liu
- Chris Wood
- Jose Karam
- Kanishka Sircar
- Pheroze Tamboli
- Rebecca Slack (Biostatistics)



- Gia Garcia
- Timothy Sargis
- Adela Ramirez Torres
- Adam Olalde



- Thai Ho



R01 CA181106
R01 CA217905

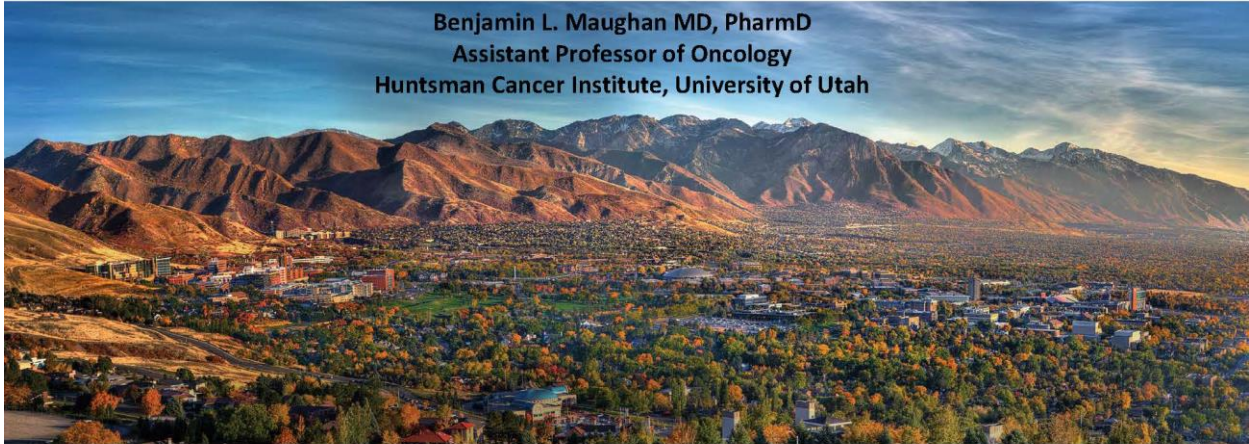
2020 Annual VHL Family Meeting
October 24, 2020

Clinical Trials Update

Benjamin Maughan, MD, PharmD

Finding Value in Targeting VHL

Benjamin L. Maughan MD, PharmD
Assistant Professor of Oncology
Huntsman Cancer Institute, University of Utah



Conflicts of Interest

Paid consultant/advisor to:

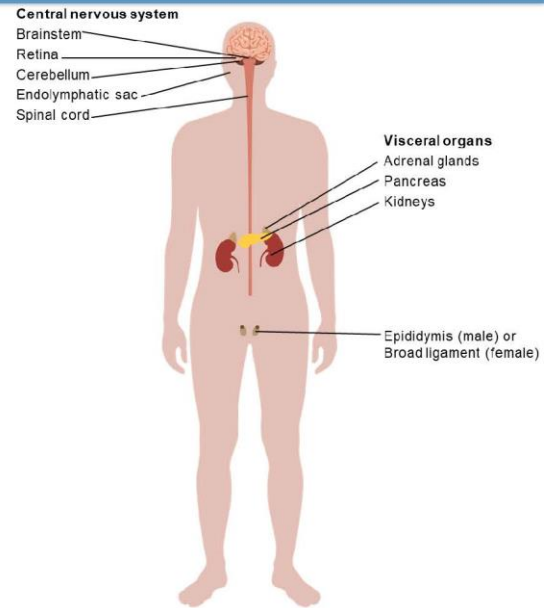
Janssen, Astellas, Bristol-Myers Squibb, Clovis, Tempus,
Merck, Exelixis, Bayer Oncology and ***Peloton Therapeutics***

Received research funding to HCI from:

Exelixis, Bavarian-Nordic, Clovis and Bristol-Myers Squibb

VHL Manifestations

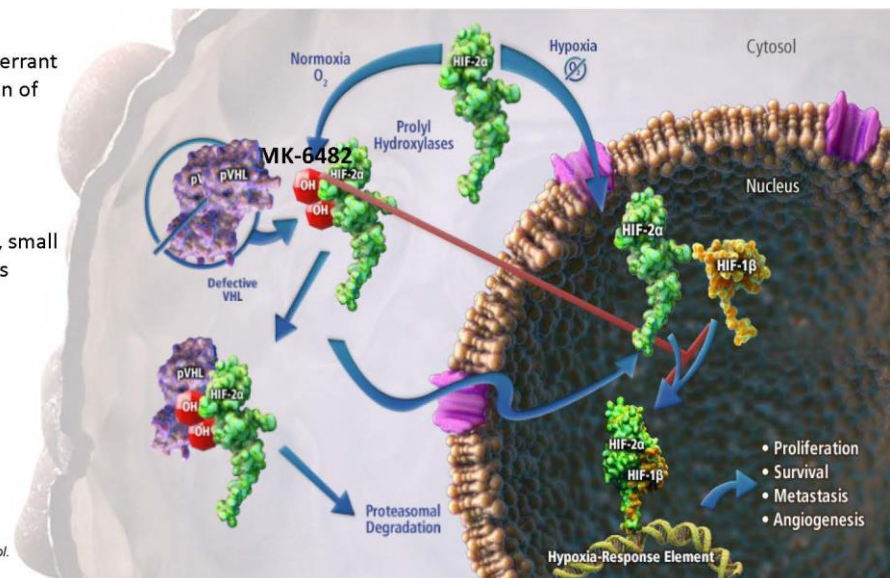
- VHL disease: autosomal dominant hereditary disorder
 - At risk for RCC, CNS and retinal hemangioblastomas, pancreatic neuroendocrine tumors, and other lesions
- RCC occurs in 25-60% of individuals and is a key cause of morbidity and mortality
- Surgery is generally considered when the largest renal tumor reaches approximately 3 cm
 - Surgical treatment is intended to decrease the risk of metastasis
 - Tumors will continue to recur, and repeated surgeries are required to control other VHL disease manifestations
- Despite aggressive treatment, life expectancy is shortened in patients with VHL disease



HIF-2 α Drives Tumor Growth in VHL-RCC

- VHL inactivation results in aberrant stabilization and accumulation of HIF-2 α ¹⁻³
 - Subsequent constitutive activation of genes that drive tumor growth
- MK-6482, a potent, selective, small molecule HIF-2 α inhibitor, has shown favorable safety and antitumor activity in advanced RCC⁴

1. Kaelin WG Jr. *Trans Am Clin Climatol Assoc.* 2017;128:298-307. 2. Kondo K et al. *Cancer Cell* 2002;1:237-246. 3. Xu R et al. *J Med Chem.* 2019;62:6876-6893. 4. Choueiri TK et al. *J Clin Oncol.* 2020;38(suppl 6). Abstract 611.



Goal of Treatment

Prevention of surgery or other procedural interventions, concurrently with prolongation of survival to match that of the normal population without VHL

Characteristics of an Ideal Prevention Therapy Strategy

- Prevention of kidney cancer metastasis and disease progression
- Effective to prevent non-kidney manifestations of VHL syndrome
- Tolerable for chronic use

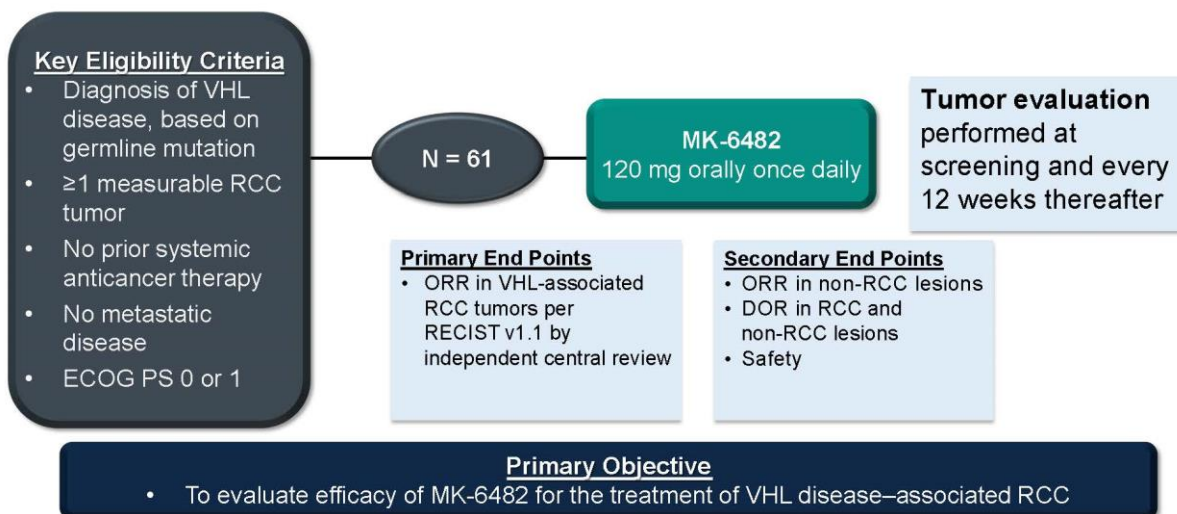
Prior Clinical Trials for RCC

Intervention	Year Conducted	Number Enrolled	Primary Endpoint	Key Secondary Endpoint	Outcome
17AAG (HSP90 inhibitor) ¹	2004-2011	9	ORR	Safety	Closed due to poor accrual
Sunitinib ²	2006-2011	15	Safety	ORR	Closed due to poor accrual
Vandetanib ³	2007-2015	37	ORR	Safety	Completed Accrual
Sunitinib ⁴	2010-2012	7	ORR	Safety	Closed due to poor accrual
Pazopanib ⁵	2012-2016	31	ORR	Safety	Completed Accrual

ORR = Objective Response Rate as defined by RECIST criteria

1. NCT00088374
2. PMID 22105611
3. NCT00566995
4. PMID 27852035
5. GU ASCO 2017

Phase 2 Study: MK-6482 for VHL-Associated RCC (NCT03401788)



Baseline Characteristics

Characteristic	All Patients N = 61	
Age, median (range), years	41 (19-66)	• Prior surgery 55 (90.2%)
Sex, n (%)		• Partial nephrectomy 32 (52.5%)
Male	32 (52.5)	
Female	29 (47.5)	
ECOG PS, n (%)		
0	50 (82.0)	
1	10 (16.4)	
2 ^a	1 (1.6)	
Non-renal cell carcinoma tumor type ^b		
Pancreatic lesions ^c	61 (100)	
CNS hemangioblastoma	43 (70.5)	
Retinal lesions	16 (26.2)	

^aA waiver was requested by the investigator and approved by the IRB before enrollment. ^bAs evaluable by independent radiology committee. ^cIncludes pancreatic neuroendocrine tumors and serous cystadenomas. Data cutoff: June 1, 2020.

Confirmed ORR in RCC Lesions by Independent Central Review

	All Patients N = 61
ORR, % (95% CI)	27.9 (17.1-40.8)
Best response, n (%)	
CR	0
PR	17 (27.9)
SD	43 (70.5)
Unconfirmed PRs ^a	8 (13.1)
PD	0
Not Evaluable	1 (1.6)

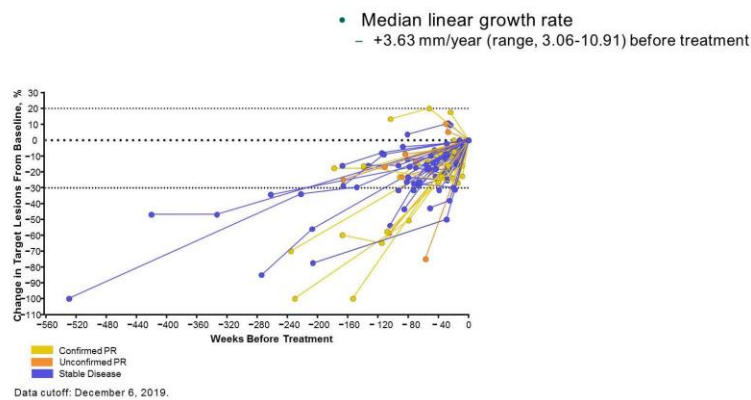
^aDocumented at 1 time point and to be confirmed at subsequent time point. Data cutoff: December 6, 2019.



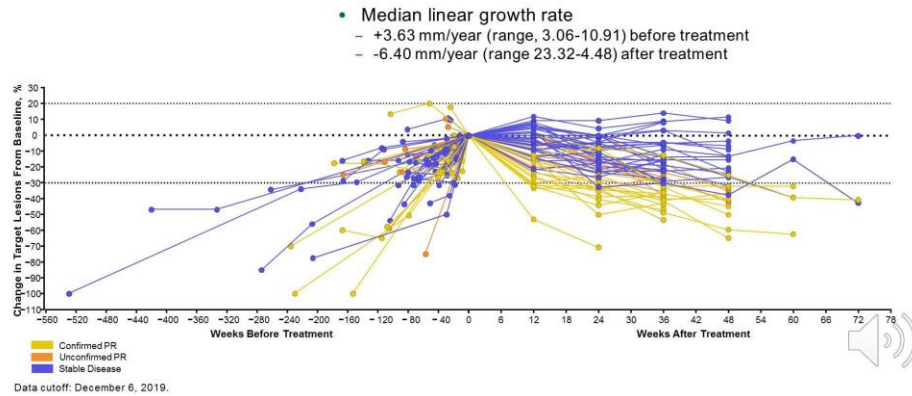
Maximum Change From Baseline in Target RCC Lesions by Independent Central Review



Longitudinal Change From Baseline in Target RCC Lesions by Independent Central Review



Longitudinal Change From Baseline in Target RCC Lesions by Independent Central Review



Adverse Event Summary

n (%)	All Patients N = 61
Any grade AE	61 (100)
Any-grade treatment-related AE	59 (96.7)
Grade 3-5 AE	12 (19.7)
Grade 3 treatment-related AE	6 (9.8)
Grade 4-5 treatment-related AE	0
Discontinued because of an AE	2 (3.3)
Discontinued because of a treatment-related AE	0
Deaths	1 (1.6) ^a
Deaths due to a treatment-related AE	0

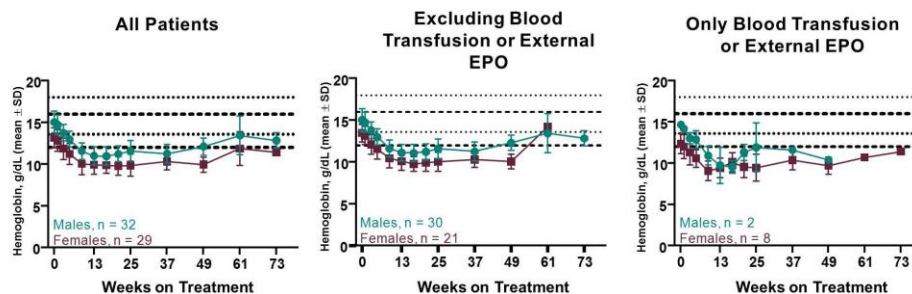
^aDeath due to AE was caused by acute fentanyl toxicity (coded as toxicity to various agents).
Data cutoff: December 6, 2019.

All-Cause Adverse Events ≥10%

AE, n (%)	All Patients N = 61			
	Any Grade	Grade 1/2	Grade 3 ^a	Grade 4/5 ^{b,c}
Anemia	53 (86.9)	51 (83.6)	2 (3.3)	0
Fatigue	35 (57.4)	32 (52.5)	3 (4.9)	0
Headache	22 (36.1)	22 (36.1)	0	0
Dizziness	19 (31.1)	19 (31.1)	0	0
Nausea	15 (24.6)	15 (24.6)	0	0
Dyspnea	12 (19.7)	11 (18.0)	1 (1.6)	0
Arthralgia	10 (16.4)	10 (16.4)	0	0
Alanine aminotransferase increased	10 (16.4)	10 (16.4)	0	0
Myalgia	9 (14.8)	9 (14.8)	0	0
Vision blurred	9 (14.8)	9 (14.8)	0	0
Constipation	8 (13.1)	8 (13.1)	0	0
Aspartate aminotransferase increased	7 (11.5)	7 (11.5)	0	0
Upper respiratory tract infection	7 (11.5)	7 (11.5)	0	0
Weight increased	7 (11.5)	6 (9.8)	1 (1.6)	0

^a1 patient was recorded as having hypoxia (grade 3).^b1 patient was recorded with retinal detachment (grade 4).^c1 patient died from toxicity of various agents (grade 5).
Data cutoff: December 6, 2019.

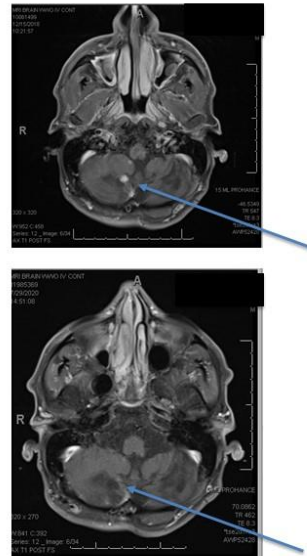
Hemoglobin Levels Over Time



Dashed lines represent upper and lower boundaries of normal values for females; dotted lines represent upper and lower boundaries of normal values for males.
Data cut off: December 6, 2019.

Non-Renal VHL Manifestations

- We are reporting our results of non-renal responses at an upcoming meeting in a few weeks (ESMO 2020)
- Anecdotally retinal, pancreatic and CNS lesions appear to be responding
- Example: Treatment response after 18 months of therapy in a cerebellar lesion



Thank You

Ernest E. Taylor, Clarence A. Taylor and
Alvida N. Taylor
Endowed Research Grant



Patients and their families



Introducing VHLA's New Executive Director

Chandra Clark



Chandra Clark joined the VHL Alliance (VHLA) in the fall of 2020. In her role as Executive Director, Chandra is responsible for continuing to lead VHLA's vision of curing cancer through VHL while providing ongoing support for patients through increased awareness, education, and advocacy.

For the past 15 years, Chandra has served in nonprofit leadership by developing innovative programs and creatively cultivating opportunities in the community to support the advancement of underserved populations. Her passion lies in advocating for equity in healthcare, education, and economic access to improve the health and well-being of under-resourced communities. Chandra's diverse professional background includes business and talent development, fundraising, marketing, and external relations with experience in collaborating with corporations and organizations to develop and implement multi-level projects, partnerships, programs, and community initiatives.

Prior to joining VHLA, she served as the Director of Community Outreach for Big Brothers Big Sisters Kansas City where she successfully launched the organization's first Community Outreach department, postsecondary education initiative, and workforce development program for youth which gained national exposure. Her previous professional experience also includes serving in nonprofit leadership at Kauffman Scholars, Newhouse Shelter, and as President and Founder of M.O.D.E.L, a faith-based organization.

Chandra holds a Master of Education degree from Rockhurst University, a Bachelor of Liberal Arts degree from the University of Missouri-Kansas City, and is a graduate of the Central Exchange Emerging Leaders Fellowship program. She has been honored to receive awards and recognitions including NextGen Leaders from the Kansas City Business Journal, Young Athena Leadership Award from the Kansas City Chamber, Rockhurst Faber Young Alum of the Year from Rockhurst University, Top Connector in Education and Entrepreneurship from the Kauffman Foundation and Most Influential Women in Kansas City Business from the Kansas City Business Journal.

In her spare time, she enjoys traveling, writing, reading, and sharing invaluable moments with her 19-year old daughter, Jada.



20 **VHL Annual Family Weekend** 20
Hosted by Huntsman Cancer Center, Salt Lake City, UT



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