VHL Alliance is dedicated to research, education, and support to improve awareness, diagnosis, treatment, and quality of life for those affected by VHL.

December 9, 2022

Ayako Takahashi MD, PhD
Kyoto University Hospital
Kyoto, Japan

Dear Dr. Takahashi,

The VHL Alliance is pleased to recognize Kyoto University Hospital as an International VHL Clinical Care Center (CCC). Your application was carefully reviewed by members of our Clinical Advisory Council, many of whom are internationally renowned VHL specialists.

To summarize the guidelines detailed in the application form, we ask each Clinical Care Center to:

- Provide your specified Point of Contact with referral criteria, surveillance protocol, and a list that contains contact information for every member of your CCC.
- Identify and implement a system to assess psychosocial needs of each patient, and check all areas of the patient's body that need surveillance. The surveillance protocol used should be the same or similar to the one outlined by the VHLA Clinical Advisory Council.
- Ensure regular communication among all CCC team members, beyond sharing electronic medical records. Communicate medical updates, including psychosocial needs, with patient's primary care clinician.
- Encourage patients to participate in VHLA's MyVHL: Patient Natural History Study (vhl.org/MyVHL).
- Renew your CCC application every 2 years. Contact VHLA if changes to your CCC occur in the interim.

VHL, BHD, HLRCC are rare and complicated diseases. As such, it is impossible to assume a CCC knows all the answers. We ask that clinicians make every effort to seek the best available information from this worldwide community prior to taking action, and to share their own experience and expertise to enrich the total knowledge base. You are always welcome to contact us via the phone (617-277-5667 x4) or e-mail (clinics@vhl.org). Members of VHLA's Clinical Advisory Council can also be contacted for additional information.

We see the CCC initiative as an essential link in the chain of information for physicians around the world, seeking to provide optimal care for people with VHL. Please help us understand how best to support you in this effort, and feel free to provide input on this program or other related issues. We can be reached via telephone (617-277-5667x4) or email (clinics@vhl.org). If you need, you can request additional resources at: vhl.org/resourcerequest.

We thank you on behalf of the VHL Alliance and for all involved patients and their families!

Sincerely,

Othon Iliopoulos, MD, PhD
VHLA Clinical Advisory Council, Chair
clinics@vhl.org

Joshua Mann, MPH
VHLA Director of Health
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CC: Point of Contact, VHL Navigator, CCC Specialists

Enclosed

VHL CCC Team Member Responsibilities

CCC Sponsoring Physician

- Ensures organization and coordination at the CCC. Designates Point of Contact and VHL Navigator and assembles team of VHL specialists. Shares VHL Surveillance Guidelines within team, ensures team members know each other, and educates team on the importance of patient participation in the MyVHL: Patient Natural History Study at: vhl.org/MyVHL.
- Ensures team members notify Patient Navigator when VHL patients are seen in their specialty departments.
- Conducts / facilitates regular communication with entire CCC team in addition to communicating with EMR. Suggestions: manages an internal list-serve for sharing observations about VHL, directs specialists toward VHLA specialty list-serves, encourages specialists to educate their department about VHL, etc.
- Promotes inclusion of VHL patients in patient meetings, (ie: cancer support groups) when appropriate.
- Arranges / participates in medical education meetings to teach physicians outside of CCC team about VHL.
- Member of "CCC Lead Team".

CCC Point of Contact

- Serves as initial contact for patients, families, and physicians. Contact info is listed on VHLA website and given to our hotline volunteers. Uses VHL Surveillance Guidelines to connect patients with relevant CCC specialists. This person should have a basic understanding of VHL (and hopefully HLRCC and BHD), but is not expected to answer any medical questions that require the patient to see a specialist.
- Ensures each CCC Specialists have VHLA Patient Natural History Study physician information sheets and patient brochures. Frequently encourages patients to participate longitudinally in the study.
- Member of "CCC Lead Team".

CCC Patient Navigator

- Personally welcomes each VHL CCC patient, introducing them to the concept of comprehensive, coordinated care within the CCC team. Flags patients' EMR records as VHL and has overview of each VHL patient's care.
- Works at the patient and institutional level to ensure that each CCC patient is adhering to the VHL Surveillance Guidelines and receiving all recommended tests and treatments.
- When feasible, works with appointment scheduling to expedite and coordinate VHL appointments.
- Has overview of each VHL patient's care. Follows up with patients that have missed any CCC appointments.
- Monitors the patient's psychosocial needs using ie: HADS. As needed, works with Specialists to establish relevant care close to the patient's home.
- Shares genetic testing / surveillance results with patient; ensures patient's PCP receives report after each CCC visit.
- Reminds / encourages patients after every clinical encounter to participate in the MyVHL: Patient Natural History Study.
- Determines if patients are facing insurance / financial barriers; utilizes the hospital's Patient Financial Services Department to assist patients in overcoming these barriers.
- Member of "CCC Lead Team".

CCC Specialist

- Adheres to VHL Surveillance Guidelines. Monitors the patient's psychosocial needs at every clinical encounter using ie: HADS; as needed, works with Patient Navigator to establish relevant care close to the patient's home.
- Encourages patients to participate longitudinally in the MyVHL: Patient Natural History Study after each appointment / procedure.
- Serves as department expert on VHL:
    - Receives notification from departmental colleagues each time a VHL patient is seen.
    - Ensures VHL Patient Navigator incorporates these patients into the CCC system.
    - Educates department on need for coordinated care between multiple specialists to properly manage VHL.
- Understands CCC structure. Knows, works with, and communicates with other team members.
- Becomes a member of VHLA list serve. Posts questions/responses to clinicians at other CCCs.
- Willing to give VHL presentations at physician and/or patient meetings when requested by the Sponsor.

Suggested Referral Criteria* for VHL Clinical Care Centers

*Developed and Used by Othon Iliopoulos, MD, PhD**, Massachusetts General Hospital, Boston MA*

1. **Any blood relative of an individual diagnosed with VHL disease**
2. **Any individual with *<u>TWO</u>* VHL-associated lesions**
   - Hemangioblastoma (HB),
   - Clear cell renal carcinoma (RCC)
   - Pheochromocytoma (PHE)
   - Endolymphatic sac tumor (ELST)
   - Epididymal or adnexal papillary cystadenoma
   - Pancreatic serous cystadenomas
   - Pancreatic neuroendocrine tumors
3. **Any individual with ONE or more of the following:**
   - CNS hemangioblastoma
   - Pheochromocytoma or paraganglioma
   - Endolymphatic sac tumor (ELST)
   - Epidiydmal papillary cystadenoma
4. **Any individuals with:**
   - Clear cell renal carcinoma (RCC) diagnosed at a < 40 year old patient
   - Bilateral and/or multiple clear cell RCC
   - >1 pancreatic serous cystadenoma
   - >1 pancreatic neuroendocrine tumor
   - Multiple pancreatic cysts + any VHL-associated lesion

These are criteria used to REFER patients. These are NOT criteria for clinical diagnosis of VHL.

* Based on Melmon KL, Rosen SW, Lindau's Disease: Review of the literature and study of a large kindred. Am J Med 1964; 36:535-617.

Suggested VHL Surveillance Guidelines

Approved by the VHLA Clinical Advisory Council - [Revised 04/24/2020]

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. Even with the VHL gene, once an individual has reached the age of sixty and still has no evidence of VHL on these surveillance tests, imaging tests may be reduced to every two years for MRI.

Revisions in this version of the surveillance guidelines for VHL include a change in recommendations from CT to MRI, in order to reduce exposure to radiation for all people. CT should be avoided for all pre-symptomatic people, and should be reserved for occasions when it is truly needed to answer a diagnostic question.

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.

Regular audiometric tests are included in the surveillance protocol to provide a reference point in case of sign or symptom of hearing loss, tinnitus (ringing in the ears), and/or vertigo (dizziness, loss of balance). If hearing drops, swift action may be required to save hearing.

MRI is the preferred surveillance method for the abdomen. Quality ultrasound may be substituted for MRI of the abdomen no more than once every two years. “Quality” is defined as a machine that produces good quality pictures, with an operator experienced in imaging the organs being studied. The objective is to find even small tumors, which are difficult to identify on ultrasound.

Type of Surveillance (Tumors being screened)	**AGE[1]**						
	Until age 5y	**Beginning at age 5y**	**Beginning at age 11y**	**Beginning at age 15y**	**Beginning at age 30y**	**Beginning at age 65y**	**Pregnancy[10]**
History and Physical Examination[2]	Yearly from age 1y	Yearly	Yearly	Yearly	Yearly	Yearly	Prior to conception[10]
Blood Pressure and Pulse (Pheochromocytomas/paragangliomas)	Yearly from age 2y	Yearly	Yearly	Yearly	Yearly	Yearly	Prior to conception[10]
Dilated Eye Examination[3] (Retinal Hemangioblastomas)	Every 6-12 months, beginning before age 1y	Every 6-12 months	Every 6-12 months	Every 6-12 months	Yearly	Yearly	Prior to conception, then Every 6-12 months[10]
Metanephrines[4] (Pheochromocytomas/paragangliomas)		Yearly	Yearly	Yearly	Yearly	Stop routine[1]	Prior to conception[10]
MRI Brain and Spine w/wo Contrast[5,6,7] (CNS Hemangioblastomas)			Every 2 years	Every 2 years	Every 2 years	Stop routine[1]	Prior to conception[10]
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[10]
MRI Internal Auditory Canal[9] (Endolymphatic sac tumors)				Once			

These screening guidelines are also available on our website at: vhl.org/surveillance-guidelines Suggested guidelines for BHD and HLRCC can be found at: BHDSyndrome.org and HLRCCinfo.org

Notes:

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 wit 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 renal lesions present on initial scan, continue routine surveillance every 2 years. If small tumors (< 3 cm) found, reimage 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).
9) 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.
10) “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.

Suggested Psychosocial Questionnaire

If your CCC decides to use another questionnaire, please provide VHLA a copy and scoring key.

Revised HADS Questionnaire – suggested 6 questions

1. I still enjoy the things I used to enjoy: (depression question)

0	Definitely as much
1	Not quite so much
2	Only a little
3	Hardly at all

2. I can sit at ease and feel relaxed: (anxiety question)

0	Definitely
1	Usually
2	Not often
3	Not at all

3. I look forward with enjoyment to things: (depression question)

0	As much as I ever did
1	Rather less than I used to
2	Definitely less than I used to
3	Hardly at all

4. I get a sort of frightened feeling like 'butterflies' in the stomach: (anxiety question)

0	Not at all
1	Occasionally
2	Quite often
3	Very Often

5. I can laugh and see the funny side of things: (depression question)

0	As much as I always could
1	Not quite so much now
2	Definitely not so much now
3	Not at all

6. I get sudden feelings of panic: (anxiety question)

0	Not at all
1	Not very often
2	Quite often
3	Very Often

All items scored 0-3 (where 3 is most severe). Alternate items group into Anxiety / depression subscales. Please note that this questionnaire was validated using 12 questions. Totals for each subscale are categorized as follows:

0-3	Normal	
4-5	Mild	Possible clinical disorder
6-7	Moderate	Probable clinical disorder
Above 8	Severe	