VHL FAMILY FORUM

Family, Friends, Physicians, & Researchers dedicated to improving diagnosis, treatment, and quality of life for people affected by von Hippel-Lindau.

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Understanding How Genotype Influences Phenotype

by Sarah Nielsen, Genetic Counselor

Editor's Note: *The "genotype" is the makeup of the altered genes – where is the alteration in the gene? – and the "phenotype" is the set of symptoms and tumors experienced by a person with that genotype. By studying how families and family members are the same or different, we are learning more about how the VHL protein functions in the cell connecting with other proteins and enzymes to regulate normal processes, and what happens when one of those connections is changed.*

Von Hippel-Lindau (VHL) disease is what is described as an inherited endocrine tumor syndrome. Breaking this down, it means that VHL is passed down in families and causes an increased risk for a variety of tumors that may be cancerous or not, and can occur in endocrine glands (whose job is to produce hormones) as well as non-endocrine organs. Some examples of organs that can be affected by VHL-related tumors include the kidney, adrenal glands, pancreas, eyes, brain, and spine. VHL has 90% "penetrance" by age 65, which means that if you have an alteration in the VHL gene, there is a 90% chance that by age 65 you will have shown at least one symptom. This paper focuses on one specific type of VHL, type 2A, which is usually associated with a high risk for adrenal gland tumors (called pheochromocytoma, or "pheo"), eye tumors (retinal angioma, or "RA"), and brain/spine tumors (hemangioblastoma, or "HB"), and a low risk for kidney and pancreatic tumors. Specifically, the paper takes a closer look at pheochromocytoma, the most common tumor type in VHL type 2A. Pheo is a very dangerous tumor that can become cancerous. Even if it doesn't metastasize, if it is left untreated, it can result in death due to complications of severe hypertension (high blood pressure).

VHL disease is caused by a mutation, or change, in a gene called a tumor suppressor. Genes are like packages of information that tell our body how to function and determine what we look like. Tumor suppressors are specific types of genes that prevent tumors from forming, so when there is a mutation in the gene, it is more likely that tumors will develop. The gene that causes VHL is also named VHL and is located on chromosome number 3. We receive two copies of each of our 23 chromosomes, one from our mother and one from our father. It only takes a change in one of our chromosome 3s to have VHL disease. This study compared two very large families with VHL type 2A that both have German ancestry (from different regions of Germany) and have settled in the Western Pennsylvania area.

Although the families have the same type of VHL, they have different mutations in the VHL gene. They both have "missense" mutations, which means only one nucleotide, or letter, has been changed in the spelling of the gene, but those letters are different in each family. Both "misspellings" prevent the VHL gene from doing its job and result in an increased risk for the tumors associated with VHL type 2A. The mutation in Family 1 is called Y112H and the mutation in Family 2 is called Y98H. These are the two most common mutations found in VHL type 2A families. This paper looks at how these different mutations might result in differences in how the disease is expressed, especially related to pheo.

Because members of both of these families had been followed for decades at the University of Pittsburgh, and their VHL-specific medical and genetic counseling records were available for review, family members were re-contacted and extensive

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interviews were conducted. After all the relevant information was collected, pedigrees (family trees) were constructed for each family. All the members with VHL were tabulated, noting which types of tumors had been diagnosed and at what age. Then the characteristics of the pheos diagnosed in each family were examined more closely with regard to specific clinical and pathological features, such as the age at first diagnosis, chemicals produced, number, location, size, and weight, and what the tumors looked like under the microscope.

It was discovered that the overall expression of the disease was very similar between the families. In Family 1 (Y112H mutation), out of 108 family members determined to be at risk, 49 members were confirmed to have VHL (45%); 71% of these individuals have shown at least one symptom of VHL. Pheo was the most frequent tumor type (86%), followed by RA (37%), HB (17%); there was only one case of kidney cancer. Similarly, in Family 2 (Y98H mutation), 65 out of 131 at-risk members were confirmed to have VHL (50%); 72% have had at least one symptom of VHL. Pheo was the most frequent tumor type (79%), followed by HB (26%), RA (19%); again, there was only one case of kidney cancer.

Differences between the families were discovered regarding pheo expression. The most significant differences were that the average age of pheo diagnosis was 9 years younger in Family 2 compared to Family 1 (20 years old vs. 29 years old), pheo in Family 2 was more likely to be multiple (multifocal), and pheo in Family 1 was more likely to be cancerous and result in death. Additional differences that were not as strong between the families were that in Family 1 pheo was more likely to be diagnosed by symptoms rather than routine screening and additional pheos were diagnosed sooner after first diagnosis; in Family 2, pheo was more likely to be found outside the adrenal glands (a special type of pheo called paraganglioma). Size, weight and frequency of left- or right-sided pheos were found to be the same between the two families.

The limitations of this study are that, although the families were large, it is still a relatively small sample size, so we cannot say that these findings hold true for all families with these mutations. Also, because there were many members in each family, we could not ensure that they were all followed properly regarding their VHL, and some members did not always come on schedule for their screening tests. Some information used in the study was verbal and could not be verified by medical documents. Lastly, we were unable to take into account environment and lifestyle differences between the families that could have contributed to the differences observed.

The take-home points of this study are multiple:

1) it is important to screen for pheo beginning in childhood (pheos occurred as early as 6 years old in the study);

2) children who have pheo or paraganglioma should be tested for VHL gene mutations;

3) if individuals with a Y98H mutation have abnormal blood or urine, they should have a special type of body scan (called a MIBG scan) that is able to detect pheos that occur outside the adrenal gland; and

4) it may be beneficial for individuals with a Y112H mutation undergoing surgery to remove a pheo to have an "open resection," which is more invasive than a "laparoscopic resection," but is more likely to remove all of a pheo that may be cancerous.*

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*Nielsen SM, *et. al.* Genotype-Phenotype Correlations of Pheochromocytoma in Two Large von Hippel-Lindau (VHL) Type 2A Kindreds With Different Missense Mutations. *Am J Med Genet A*. 2011 Jan;155A(1):168-73. PMID: 1204227

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National Conference in Houston

SAMPLE TOPICS:

Advances in treatment of ELST and hemangioblastomas
New clinical trials opening
Using genetic information to manage your health

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Interview with Trisha Torrey

by John Novack, Dir. of Communications, Inspire.com

Periodically, we at Inspire interview people we feel are making contributions to helping patients worldwide. To kick off this feature, I spoke with patient advocate and author Trisha Torrey (www.everypatientsadvocate.com), a nationally recognized writer, speaker and workshop teacher on issues related to patient advocacy. A former marketing executive, Torrey became a patient advocate after enduring a misdiagnosis of cancer in 2004. She is the author of the book, *You Bet Your Life! The 10 Mistakes Every Patient Makes (How to Fix Them to Get the Healthcare You Deserve)*.

Trisha Torrey

John Novack

Inspire: Amid all increasing references to "epatients," you use a term, "em-patient," for "empowered patients." Why "em-patient?"

Torrey: I spent 20-plus years as a marketer, long before I thought I'd have anything to do healthcare. The only reason I have anything to do with healthcare is that I had my own run-in with the system. As a marketer, you always want words to have the same meaning to everybody. But the word "epatient" could be interpreted differently because of the "e" in front of "patient." Email, e-commerce, it has to do with being on the Internet, right? Being online and learning things online is a subset of everything that it means to being an empowered patient.

Inspire: Being able to go online for resources and support is key, though, correct?

Torrey: Well, the reason I use the term "em-patient" is because I'd like to see something that encompasses the entire experience, which includes how you communicate with your providers, to ensuring that you're safe in the healthcare, to how to look things up online and make sure it's credible information. Patients who aren't online don't have to feel left out.

Inspire: We see a challenging paradox in which patients want to feel empowered, want to be on more of an equal footing with their caregivers, but it's tough to rise to that challenge when you're ill, regardless of your education, your support structure, etc., true?

Torrey: When you're really sick, when you've just been diagnosed, when you're really afraid, you likely don't have the wherewithal to be an empowered patient. My example is, say that I just got diagnosed with cancer. I'm upset, I'm afraid, I have a million questions, but at the moment I can't cope with my own emotions, let alone handle additional information. So I come home and stew with the emotion for a period of time. Now, for some people in that situation, that's going to take a few hours, for others, it's going to be a few months. Until they get past that emotion, they're not going to be able to do anything to empower themselves around that one particular diagnosis.

Inspire: It's not an all or nothing situation though, correct? "You're an empowered patient or you're not," is not what you're saying.

Torrey: Not at all. That's not to say they haven't been empowered before. A long-term diabetes patient, for example, who has taken control of their diabetes, if that patient gets a cancer diagnosis, for the moment, she's not empowered about anything having to do with the cancer. So, until they're ready to deal, they're going to look to some other way, like a family member helping out, or they have to just depend on their doctor, or they have to hire an advocate. But I suppose that is what empowered really means—and that is where you are in any given moment, knowing there are tools out there to help you. You just have to choose the right ones at the right time.

Inspire: In the Inspire community there is some sharing of clinical information and some guidance on selecting clinicians, but there are very many discussion strings that are underpinned chiefly by statements of empathy and understanding that a fellow community member is hurting. And those statements, seemingly simple, are extremely powerful. Does that surprise you?

Torrey: "We hear you, and we care, and we will fill in the gap when you need us," are powerful magnets. I think there are a couple of aspects to all of this. First, one of the big things you're talking about is the difference in the way women and men communicate. There are studies that have been done on this, but the basics are that women, when they reach out to someone, what they're looking for are those comforting noises. And those comforting noises say, "You're not alone, you're not the first

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person who has had to deal with this, and therefore there might be some answers for you, and number three, we're here for you when you need us."

Inspire: And men?

Torrey: On the other hand, men, in that kind of outreach, are looking for someone to provide them with solutions. When you're dealing with emotions like fear, sadness, or frustration, those are like holes that need to be filled. You've heard about this in breakups in relationships, and all of a sudden there's a hole in your emotions that needs to be filled, and that's why people get married a second time too fast, or they get into things that they shouldn't be involved in, because rather than dealing with the emotion, they're looking to fill the void. I think that's a lot of what communities do. They rush in to fill those holes, those voids. If I've been diagnosed with a disease, and my body has basically betrayed me, and I need something to fill that void, if it's 14 people in an online community saying, "We are so sorry and we're here for you," that helps me fill the hole—even if it's temporary. It helps me to know I'm not in it alone.

I don't know if this would have been as effective 20 years ago, when we were still operating under the paternalistic and benevolent "Marcus Welby, MD" model.

Inspire: How so?

Torrey: Then, we didn't need as much other support from outside sources. The doctors then made you feel like you were being supported. There was a greater sense that your doctor was more empathetic. Now, too often, it's this cold scientific approach, like, "Well, we ran the test and I'm sorry to tell you you've been diagnosed with 'x' disease, and what that means is you'll have to come back here and we'll start treatments," and so forth. It's an entirely different conversation than years ago. Nobody's helping deal with the emotions yet. And patients have to do that first.

Inspire: Back to the topic of patients researching their medical conditions, or caregivers doing so for their loved ones. How can patients be more effective in communicating research they've found with their physicians?

Torrey: Fair or not, physicians' time is constrained, so the first thing you want to do is to acknowledge to your doctor that his or her time is constrained. Saying this takes the docs off of the "time defensive," where, if they see you carrying a raft of clinical papers printed off the Internet, they're thinking, "Oh my God, I only have four minutes with this patient and I'll never be able to have this conversation with this patient and get on to my next patient." So, an acknowledgment of the short time is a good way to start.

Inspire: Let's say you get good feedback from that opening discussion. What next?

Torrey: I tell patients to not show up with printouts from the computer. Do not. Be well enough versed in what the printouts say that you can carry on the conversation. Walking in the door with the raft of papers from the Internet is the visual clue to the doctor that there's going to be a problem with your meeting. From the doctor's point of view, he or she has had years of medical school and training. If you show up with information from the Internet and just present it like that—that comes across as if you are saying that your hour on the Internet is equivalent to their years of medical school and their experience. Now, your investment in your disease or condition certainly is as big, if not bigger, but your experience with it is not.

Inspire: Perhaps there is information you got off the Internet that's valuable, though, and it's tough to memorize it and be able to discuss it with your doctor.

Torrey: But the minute you show up with a bunch of printouts, most doctors will go on the defensive, and that's not where you want to start a conversation. A way to approach this issue is to say, "What do you know about 'x' topic?" and let the doctor respond. If the doctor says that he or she had never heard of that topic before, then you can say, "I found information about it and I'm trying to gather more information because it's something I'm interested in." If the doctor discounts the topic as it relates to your medical situation, for whatever reason the doctor does that, then listen to your doctor. It's not that you wouldn't do more research on it; it gives you a better sense of where you stand with your doctor on that particular topic. If you just begin the conversation in that way, it's an acknowledgment that the doctor has that much more experience with something than you do, but you still have information to discuss with your doctor.

Note: Torrey blogged on About.com about the topic of doctors and the Internet. Go to http://bit.ly/fdLRHv to read that blog post. She also wrote about her definition of "em-patient," which you can at http://bit.ly/ejSpwf. Hear her interview with Joyce at powerfulpatient.org.

Join the fun in Houston!

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Jordan's Story

By Elizabeth A., Washington

I am a recent graduate from Washington State University and it was there that I met my current boyfriend, Jordan. I don't know that words can truly do him justice, but I'm going to give it a try.

Jordan and I met freshman year while we were living in the same dorm. I was immediately drawn to his warm smile and quiet confidence. He was kind to everyone around him and people loved to be in his company. We dated for a while but ultimately decided neither of us was ready for anything very serious. In the next few years, Jordan's father had a long stretch of medical procedures due to VHL. He had to receive brain surgery multiple times and had ongoing kidney complications. Jordan moved across the state home to Olympia, Washington, in part to take care and be available for his father.

Jordan and Elizabeth

It was the summer before my senior year that we reconnected with emails and phone calls. Jordan was the same amazing person as before, and this time I was ready for him. It has been in these past nine months that I have gotten the full story of VHL in his family and how it affects them.

Jordan is the second of three children with a father affected by VHL. Jordan has had tumors in his eyes removed and undergoes regular screenings. I have had the pleasure of meeting his family and can see the difficulty his father is having. It breaks my heart to see his family in pain both by the day-to-day struggles and the uncertainty of the future. Although I can't imagine such a hardship, they take it in stride. They are warm and funny and are constantly looking on the bright side. Jordan focuses his energies on his family and on me and to say I was inspired by their strength would be an understatement.

As a science major, I could not help my curiosity and dove head-first into journal articles about the disease. I still speak with professors who help me work through the jargon of the medical research community, and I am hoping to expand my understanding of the cellular mechanisms for the disease. I wanted some way to show Jordan my support and to help in a tangible way. Jordan was familiar with VHL Family Alliance, and when I proposed to run the Seattle Half Marathon to donate to charity, it was the VHL Family Alliance that came up first. I sent out emails to my family and friends and set up a website: http://www.firstgiving.com/elizabethaultman.

On November 28th, I ran the half marathon wearing a shirt I had made simply with the name of your organization on it. I hope in the future to be able to do and understand more. I love him so much; he and his family have changed my life, and I want to do everything in my power to help.

Conquering Cancer:
Joining Science and Engineering

by Joyce Graff

On Wednesday, March 16, 2011, I attended a conference at the Massachusetts Institute of Technology (MIT) as part of their celebration of the 150th anniversary of MIT. The conference, "Conquering Cancer through the Convergence of Science and Engineering," was a fascinating day of talks organized by Tyler E. Jacks, Director of the David H. Koch Institute for Integrative Cancer Research at MIT.

It was a very impressive roster of speakers, including multiple Nobel Prize winners, and a powerful display of the Koch Institute and MIT. As Dr. Jacks said, he feels that MIT is now in the right time and the right place to finally make significant progress in the War on Cancer. Time because of the maturation of technologies like miniaturization, battery life, and nanoparticles; place in Boston and MIT, surrounded by some of the finest hospitals in the world, by numerous pharmaceutical companies large and small, and by many innovative startup companies.

In 2002, cancer became the leading killer disease in the world—surpassing tuberculosis, malaria, and HIV. 70% of the cases of cancer will emerge in the developing world, offering another layer of difficulty in providing care. For millions of people in the world, it takes longer than one day to get to a doctor, even in major cities.

Cancer is primarily a disease of age, as it takes time to accumulate the genetic damage or "hits" that lead to cancer. Part of the problem is our success in increasing longevity. In 1910, the average life expectancy in the United States was 45. As we live longer, our risk of cancer rises. Now, with an average life expectancy

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Conquering Cancer

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many decades beyond that, the rates of cancer rise with the average age of the population. Our challenge is not only to extend life, but to extend the time in which we enjoy wellness before cancer risks rise.

Some of the key problems to be conquered in cancer are:

- Prevention
- Vaccines
- Mechanisms of delivery that can transport medications to specific microscopic areas
- and in particular, Delivery to poorly vascularized areas

These challenges are not entirely medical. They also need the problem-solving abilities of engineers, physicists and chemists—many of the skills for which MIT is also famous.

When drug is injected into the body, only about 1% of the drug makes it to the tumor of interest. Dr. Robert S. Langer showed us the nanoparticles he designed to treat cancer. These are particles about the size of three protein molecules, "decorated" with a molecular zipcode, a peptide seqence that attaches to the surface. In order to further increase the amount of drug delivered to the tumor, they can use two kinds of particles—one to attach to the tumor and serve as a beacon to attract more of the drug-bearing particles*.

Dr. Joseph DeSimone, Professor of Chemistry at University of North Carolina, shared with us some of the innovations now available to medicine thanks to colleagues in other sciences: an electrode delivered by a catheter into a pancreatic cancer tumor, infusing the tumor with biologics to intensify the effect of the drug on the tumor while limiting the side effects. He has invented a new way of creating nanoparticles that are not only small, they can be produced in a particular shape that will allow them to enter the cell and bind with specific proteins in the body. There are significant challenges in getting experts from various scientific disciplines to work together—they have different backgrounds, basic principles, and enormous differences in vocabulary. But it's exciting. Biology is a different science from physics and chemistry, where you can identify, quantify, and establish laws. In biology, we don't always know what the variables are, or how to control them. Identifying and cataloging those variables is helping to put us on the right path. For engineers, it is uncomfortable and also exciting to model systems with analysis of multiple unknowns.

*See Nova's interview with Dr. Langer and their animation of this invention. http://www.pbs.org/wgbh/nova/tech/making-stuff-smarter.html especially (minutes 40–45).

Partners in Research:

Data Sharing, Privacy, and Consent—Changing the Conversation

by Joyce Graff based on the Minutes of the DCLG meeting

A group of sixteen patient advocates from around the country who form the NCI Director's Consumer Liaison Group (DCLG) met in February 2011 to study the issues in making patient tissue and data more available for research toward a cure for cancer.

Currently, data is collected on a project-by-project basis. Patients are asked to provide information during the course of a project, including some medical history information. This information is often scant, based on patient memory and notes, not on the actual detailed medical records. One patient's records may be scattered among many hospitals, in many states, mostly on paper, and mostly inaccessible.

Patients provide information to the project, which is then owned by the institution where the project is based. It is not "owned" by the researcher, and no longer "owned" by the patient. Under the law, it is "owned" by the institution. If another similar project is launched, even if the research team and institution are willing to share, the incompatibilities of their record-keeping systems often pose additional barriers to sharing. If the information is computerized, the technical difficulties could potentially be overcome with investment in bridging the two computer systems, or there may be additional technical or policy barriers. As a group, the DCLG believes that researchers, patients, and advocacy organizations must work together to find workable solutions to these challenges that meet the needs of all the people interested in moving the research forward.

Informed consent and privacy are complicated issues, and the many dissimilar efforts to solve these problems have complicated it further. The goal here is to protect the privacy of the individual while furthering research. We must all keep our eye on that goal. If we advance research while not protecting the patient from the misuse of his or her information, we have not done the right thing and have created mistrust among the patients. And similarly, if we protect the privacy of the patient by impeding research, then all of us lose. Patients and researchers

should agree on this one common goal and work together in an atmosphere of mutual respect and partnership to achieve it. We cannot learn without data. We cannot achieve research goals without the active participation of the widest possible group of participating patients from all walks of life.

Most of the conversations currently under way are focused on small changes to the current way of doing things. This limits the conversation. We need to step back and take a broad "systems" view—not just how this screw fits into that bolt, but how the total engine works, or even: is there a better engine altogether? We don't really care about any particular process, we care about how the job gets done. And the job is bigger than any one institution or any one patient.

If we simply focus on how a given institution can protect the patients, we are not getting to the bigger problem. If we simply focus on patients' rights without worrying about the impact of such rules on the progress of research, we are not getting to the bigger problem. The bigger problem is: how to we cure cancer?

Here is one version of the vision. Let's take any one question in cancer. We have a group of people who have that particular kind of cancer. We see them at or after they have been diagnosed with that cancer, and we try various kinds of treatment with them.

Would it not be useful if we could look back through their medical records and find the earliest time they reported symptoms that might have been foreshadowing that cancer? Perhaps we could see the details of their Complete Blood Counts (CBC's) over the last 10 years, and see how that has evolved. Were there early signs that we didn't know at the time might be telling us there was trouble brewing? Could we use that knowledge to identify people at earlier stages?

There are questions, for example, about the long-term effects of having a number of radiation-based diagnostic imaging tests and/or radiation treatments. Do those add up? We see long-term survivors of radiation treatment who now have leukemia or other secondary cancers. But can we look back and see the dates and details of the radiation doses they received so that we might be able to compare the total accumulated dosages of radiation over time. Currently that information is rarely recorded, and if it is, one institution keeps it in a different way than another. Most of the time, they simply say that the patient had a CT and here are the images, and of course the images are held by the institution where the scan was performed. The patient is expected to ask for them (if desired) and keep their own file of mammoth films and now CD's and written reports, but rarely are the actual radiation dosages even recorded.

Electronic health records are one step. At least if information is captured in a computer, it is easier to search it. Nonetheless, computerization alone is not the end of the conversation. The systems used by the various institutions need to interoperate in order for one patient to be able to collect all of his or her records in one place. If you move from one city to another, can you take your records with you on a CD? Wouldn't that be nice! Even within one city, one doctor may or may not be able to access the scan you had last week at the other hospital.

As patients and advocates, we have the opportunity to move the conversation out of the institution and into the advocacy community. We don't really care what system a given institution chooses. We care that each one of us can see and touch our own records—all of them—and can bring them together, make them available to the next doctor, or to the Emergency Room physician when we are on a trip. The technology is there to make that possible. We need to insist on it.

As patients and advocates, we have the opportunity to move the conversation out of the institution and into the advocacy community.

We also have the opportunity to take ownership of the collection of patient information needed to work on our disease of interest. Instead of asking patients to provide access to their data to a particular research team or institution, putting that data now under the "ownership" and policy constraints of that institution, perhaps we could ask the patients to provide access to their data to an advocacy group which then is authorized to provide access to a research team for a given purpose, without disclosing the identifying information for the participants, but with the ability for the advocacy group to go back to the participating patient and ask additional questions or suggest a clinical trial that might be of interest. The advocacy community has the opportunity here to unlock patient data resources for research. This is one of the goals of having the VHL Research Database. Please participate in this effort. See http://www.vhl.org/research/resdb.php or request a paper copy of the questionnaire on page 15.

It is critically important to engage the patients themselves in research. Without the patients, their tissue and their information, there is nothing for the researchers to study, and no progress can be made on the diseases we so desperately want to cure. While there are still many problems in the way, the energy, intention, and creative thinking of

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Partners in Research

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the patient community can help to reach above the current mass of details—getting us out of the weeds and focused on the real problem of curing cancer and other diseases. Please help by contributing surgically removed tissue to our Tissue Bank. You can register now to get the paperwork accomplished. Then before any surgery, please contact the VHL Tissue Bank at NDRI and let them know the surgeon's name and the date of the surgery. To good folks at the NDRI will take it from there, arranging for pickup of the tissue, preservation in the proper method, and conveyance of the tissue to the Bank and to the appropriate research team. Prior arrangement is critical, as samples need to be flash-frozen within minutes of removal from the body in order to be of good quality for modern research. Write to bank@vhl.org or phone 800-222-6374 to get the latest copies of the required forms.

The DCLG are your representatives to the National Cancer Institute and the National Institutes of Health, working to move from today's fractionated environment to an environment where the lifelong medical records of a large number of people with VHL or other diseases—starting long before the first tumor emerges—will be available for study in a way that protects your personal privacy, but gives researchers the perspective needed to prevent, diagnose more promptly, and treat more effectively the tumors of tomorrow. Not only is this important to research, it will be of enormous benefit to each individual to understand the trends in their own medical data, and use that knowledge to optimize their own health.

Radiation Exposure and CT Exams

By Joyce Graff, Director of Wellness at the VHL Family Alliance, vhl.org

I was privileged to attend the conference "Management of Radiation Dose in Computerized Tomography: Toward the Sub-mSv Exam", held by the Coalition for Imaging and Bioengineering Research (CIBR) in Bethesda, Maryland, February 24–25, 2011. Most of the 140 attendees were radiologists and medical physicists from major medical centers, scientists from imaging manufacturers, and representatives from regulatory agencies (FDA, NIST, etc.). I was one of five consumer advocates at the meeting.

The goal of the conference was to discuss ways to reduce the total radiation dose required during one CT examination to below 1 milli-Sievert of radiation per examination. The group was earnestly focused on providing "the right scan to the right patient at the right dose." Please note that there was no discussion at this conference of the use of ultrasound or MRI—this group was entirely focused on optimizing the use of CT technology.

First, what's a Sievert? The measure of the radiation dose in milli-Sieverts (abbreviated mSv) was defined in 1979 to allow physicists to compare the amount of energy deposited in the human body by exposure to ionizing radiation, across machines and methodologies. It is named for the Swedish physicist Rolf Sievert (1896–1966), one of the pioneers of medical physics. http://www.sizes.com/units/sievert.htm.

To put that into perspective, background radiation (walking around in your city) gives you about 3 mSv per year. A flight from New York to San Francisco delivers 0.03 mSv.

Why, one might ask, would I even sign up for such a conference? As a patient advocate, I represent people who depend upon medical imaging to manage their health.

We have long asked how all that radiation exposure may be cumulating, adding up, and potentially affecting our long-term health.

In the "old days," before medical imaging was available, in order to see how big a tumor was or how threatening, one had only one choice: do "exploratory surgery", remove the mass, put it under the microscope, and decide. Much of the time the tumor was benign, other times it was malignant, or when it was hard to make that decision in the operating room, the surgeon removed more rather than less to be on the "safe side." This resulted in a great deal of excess surgery (e.g., to remove a benign tumor), subjecting the patient to pain, suffering, infection, and general wear and tear. In the VHL community, where people deal with multiple tumors over the course of their lifetime, this took an awful toll. The surgery was often clearly necessary, but would have had an even better outcome if we had known enough to do it earlier, before it reached crisis proportions.

Using medical imaging, we are now able to track the development of tumors, watch their threat level, analyze their nature with relative confidence, and "choose the optimal moment" for interventions, remove tumors when necessary, stretch the intervals

between surgeries, and most of the time avoid surgeries for benign conditions. That does mean that people in our community may have had 1–4 CT's every year for decades. We have long asked how all that radiation exposure may be cumulating, adding up, and potentially affecting our long-term health. The answer, even at the end of this conference, is: "we don't know."

It was a fascinating two days. Most of the details, of course, went far over my head, but I learned a great deal. The following are my observations as a patient and as a patient advocate.

The amount of radiation the human is exposed to in an examination is a function of

- The machine
- The operator and/or hospital protocol being used
- The organ to be studied
- The density of bone on the path to the organ under study
- The amount of adipose tissue on the path to the organ (the patient's body-mass index, or BMI)

The machine vendors are definitely working on it, and the latest machines from several vendors go a long way to achieving this goal. BUT the very latest round of machines, available in Europe since 2009, are still not available for sale in the United States. Why? They have not yet been approved by the U.S. FDA.

These machines have buttons, knobs, and intricate settings in place to serve the needs of academic institutions with one or more medical physicists on staff. All parameters can be adjusted to meet the needs of any possible situation. As a result, the settings are complex, and vary considerably from one model to another within a manufacturer, and even more widely across vendors.

In an environment like the Mayo Clinic, Massachusetts General Hospital, Memorial Sloan Kettering, or University of Michigan, there are 10–14 machines from 2 or more manufacturers, and of varying ages. The machines are expensive and are not "turned over" quickly. But of course in these places there are also 4–6 Ph.D. medical physicists on staff. To guide their imaging technicians, Dr. Cynthia McCullough of the Mayo Clinic showed a chart they had worked out that tells the technician what settings to use to image a particular organ on each of their machines. At Mass General there are over 300 such protocols for different diagnostic examinations.

But what about centers where there is not sufficient staff time and/or talent to work this all out? Furthermore, as one physician explained to me, what about the community hospital who has their part-time day technician, their part-time night technician, and the fill-in guy who usually works at another hospital (on a different machine) and fills in when necessary?

Dr. James Thrall of the Massachusetts General Hospital explored in depth the challenges of reducing the radiation dosage. Years ago, the average dosage for one CT exam was in the range of 20–25 mSv. The average dose per exam today is about 7 mSv (or 14 mSv for abdominal CT).

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Radiation Exposure and CT Exams

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To achieve the goal of less than 1 mSv (which is approximately what you get with three chest x-rays), the picture quality suffers. He showed pictures comparing a low-dose study today with the higher-dose studies of 20 years ago, which were in fact quite comparable. The machine improvements have improved image quality enormously at the dosages previously used, but reducing the dose today brings us back to the lesser quality seen in the older machines. "But we read them then, and we can learn to read them today," he said, distinguishing the gray-on-gray subtleties.

From a patient's perspective, that means we are dependent upon the talent and experience of the radiologist. Reading a medical image is an art, not a science. And finding an artist at a community hospital is again very difficult to do. Even getting matching readings from two talented radiologists at major medical centers is very difficult. I have experienced more than once that a patient sending copies of the exact same scan to multiple radiologists will get back entirely different readings. The number of tumors, the size of tumors, and the nature of the mass may all be read differently based on the experience of the radiologist with this particular tumor type.

Until recently, at some centers, dosages calculated for adult patients were being used also on pediatric patients. Obviously the body-mass index for a 2-year-old is considerably different than for a 6-foot 250 pound adult. There is a nationwide campaign, called "Image Gently" under the direction of Dr. Marilyn Goske of Cincinnati Chidren's Hospital, to educate radiologists about the different calculations needed to ensure that children are not subjected to too much radiation. As Dr. McCullough said, "from the neonate to the morbidly obese, the safe dosages can vary by a factor of 20." We don't need "pretty pictures" for all diagnostic tasks. Is the image sufficient to answer the presenting question?

As patients, we are often asked to repeat the same imaging study because the doctor from whom we are seeking a second opinion either cannot get access to the study done at the previous hospital, or doesn't like the image quality from that other machine. How much better it would be if there were more consistency in images from one center to another!

I raised the issue of obtaining and viewing images from one center to another. Even when you carry your CD from one doctor to the next, there are instances where the neurosurgeon spends half an hour fussing with the readability of the images on his or her computer. It would be great if there were a portable format, like a "pdf" for medical images that would allow scans to be more widely read. Evidently, there is an effort underway at the NIH to achieve this.

For those of us who have had repeated images for years, the dosages are rarely captured in the medical record. In order to study the long-term effects of radiation-based imaging, we will need to begin to capture in all electronic health records the human dose data associated with each scan. This would enable retrospective analysis of the long-term effects.

Certain genetic variations make some people more sensitive to radiation exposure than others.

Certain genetic variations make some people more sensitive to radiation exposure than others. People with ataxia-telangiectasia, for example, are very sensitive to radiation. There is an effort to produce "radioprotectors" especially for people getting radiation treatments, but for ultra-sensitive patients they might also be used for diagnostic studies. In Kerala, India, for example, where there is particularly high background radiation, adding a dose of diagnostic imaging radiation has higher impact than in other regions.

There is definitely progress being made. In cardiac imaging, several centers have already achieved the sub-mSv CT exam which does provide the requisite information, and there has also been an effort to reduce the frequency of screening wherever possible. But that knowledge is confined to the major centers and has not trickled out to most of the community hospitals. As one of the panelists said in the wrap-up session, there is still a wide "knowledge gap between the people in this room and the practicing radiologists in the field."

As Dr. Thrall outlined in his keynote address, what it will take to achieve these goals includes:

- Regulations and national standards
- Improvements in the process of FDA approval of new machine models
- Education
- Improvements in the culture of clinical practice
- Reference dosages
- Registries and tracking of dose-per-exam to confirm dosages and to allow retrospective studies.

"Medicine is a team sport," he said. "This industry touches every hospital. Dose optimization and minimization will require a blend of hardware and software improvements, and policy and practice… NOW."

And let's not forget that the patient is a member of this team, weighing the benefit/risk ratio for each

scan. Before the patient even gets to the Radiology Department there are two additional team members who are making decisions. We need to be able to articulate benefit/risk in terms that are understandable to the patient and to the ordering physician so that they can make reasoned decisions like:

- What are we trying to accomplish?
- Which kind of scan is best in this situation?
- Do I need contrast media? Do I need a scan before and after contrast (doubling the radiation dose)?
- What is the exposure to radiation?
- What will it tell us?
- Is there another medical test that will give us equivalent information?
- Can I afford this?
- Will my insurance company pay for it?
- Can I afford the time away from work or family?
- Am I willing to put myself into that tunnel?
- My child breaks into tears at the thought of yet another scan. Can I do this to him? How important is it really?

With the increasing availability of Magnetic Resonance Imaging (MRI), we should encourage the use of MRI rather than CT wherever possible. This is a discussion which has to happen in the office of the prescribing physician, not in the Radiology Department. I would encourage patients to engage their physician in this discussion. As the decision is made among x-ray, ultrasound, CT, and MRI, the focus should be on how best to answer the diagnostic question while minimizing exposure to radiation—and that should include a serious look at whether an MRI might not be a better choice.

Genetic Non-Discrimination is Now Law

Adapted from an article by Tim Doran, The Bulletin

Congress passed Genetic Information NondiscriminationAct (GINA) in 2008, making it illegal for employers to request, require, or purchase genetic information, and prohibiting discrimination in health insurance coverage.

The Equal Employment Opportunity Commission (EEOC) adopted rules for the employment portion in November 2010, and they became effective in January 2011.

Genetic research has advanced quickly over the past 20 years. Scientists mapped out the human genome, which equals all the genes that make up humans, in 2003.

These advances, which prompted the law, make it possible for people to learn their potential to develop certain medical conditions based on their family histories.

Treatment for some conditions can be costly, so concerns cropped up about the potential misuse of genetic information by insurance companies and employers, many of which pay for their employees' health insurance, according to Miranda Grier, who teaches employment law at the University of Oregon School of Law.

For example, she said, to keep costs down, an employer might decide not to hire employees if they or their family members have the potential for certain medical conditions.

"Employment should be related to a person's performance on the job," Grier said.

While genetic employment discrimination has not generated a large number of lawsuits, Grier said, it is a concern, especially as the public becomes more aware of genetic research.

The law covers businesses with 15 or more employees, along with labor unions, employment agencies and apprenticeship and training programs, and it protects individuals or family members, including fetuses or embryos of those receiving fertility treatments.

GINA defines genetic tests as those that reveal, for example, a predisposition to breast cancer, colon cancer, VHL, or screening for cystic fibrosis or sickle-cell anemia.

Employers are permitted to test workers to determine if they have alcohol or illegal drugs in their systems. But they cannot test for employees' genetic predisposition to alcoholism or drug abuse.

The law allows several exceptions when obtaining genetic information would be allowed. They include:

- Overhearing the information inadvertently, or in a casual conversation, although probing follow-up questioning would be prohibited.
- Employees' participation in voluntary wellness programs, provided employers cannot access the information.
- Obtaining medical conditions to verify the need for leave under the Family and Medical Leave Act.
- Learning the information from publicly available sources, such as television, the Internet or publications.

Similarly, the law allows exceptions when disclosing genetic information would be allowed. They include:

- When it is requested in writing by the employee.
- When giving it to a health researcher.
- If it's in response to a court order.
- When it is requested by government officials investigating compliance with GINA.

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Genetic Non-Discrimination is Now Law
Continued from previous page

While this is a new step for most states, employers in Oregon will see little change according to Grier. "I think that it fits right in with the system employers use in [following] the Americans with Disabilities Act and the Family and Medical Leave Act," she said.

Based on an article by Tim Doran in The Bulletin, Bend, Oregon, January 2011 http://www.bendbulletin.com.

Minnesota Chapter Report

By Emily Pallansch, us-mn@vhl.org

I have recently taken over the job of chairman of the Minnesota Chapter from Sarah Simpson. Minnesota has a great "core group" of about 10 families that keep in contact and get together. There are a few more that I keep in contact with, but they are not close to the Minneapolis area, so they are not available to get together for meetings.

For many years the chapter has held an annual BBQ in the early fall. I hope to have a get-together this summer. I want to meet everyone.

Members share the names of providers they have used with success. I have been busy working on Minnesota provider lists and working with Mayo Clinic to educate people about VHL. Mayo Clinic is creating a website for their VHL clinic, and I am hoping to link to the VHLFA website on it.

I am looking into some ideas for fundraising. Last year the Minnesota chapter helped to fund Dr. Bratslavsky's attendance at a kidney cancer conference in Moscow, teaching doctors in Russia about VHL.

I have been in contact with numerous doctors, nurses, medical professionals about VHL and VHL Family Alliance. I have asked them if it is okay for me to place them on a Minnesota providers list. There are also a lot of doctors, nurses and medical professionals in the Minnesota database. Because we have Mayo Clinic in our backyard, there is a lot of professional medical participation. We are lucky to have Mayo Clinic in our state.

I like the idea of doing both nationwide and regional meetings. I appreciate the quarterly teleconferences for chapter leaders. I would be interested in knowing what chapter chairs in the Midwest are doing. I am close to South Dakota, Wisconsin and Iowa and would love to be in touch with their chapter chairs. The online discussion group for members has also been wonderful.

I look forward to working more with the wonderful group in Minnesota, and with our colleagues in other nearby States. I hope to meet other chapter leaders in Houston in June!

Dutch VHL Annual Meeting

by Dr. Rachel Giles, Chair, Netherlands

At our Annual Meeting on March 19, 2011, over 80 people gathered in the central town of Breukelen (Brooklyn's name source). Volunteers provided free childcare for kids that varied in age from 8 weeks to 10 years. After the opening business meeting, our former chair, Evert Ruis, gave a short presentation on the history of our organization and showed photos of meetings dating back to 1997. Two actresses/comedians—both former nurses—then performed skits, which started off with a rap about VHL. They had done their research well enough to rhyme lyrics with "pheochromocytoma"! They also acted out a doctor-patient discussion where the audience called out instructions to improve communication. Also, there was a scene depicting the awkwardness of discussing a health problem with someone you don't know well that had us doubled over in laughter.

Dr. Marina Marinkovic, an ophthalmologist from Leiden University Medical Center, gave an outstandingly clear lecture on current treatment options for VHL-related retinal angiomas. Oncology dietician Jeanne Vogel, 2010 winner of the prestigious

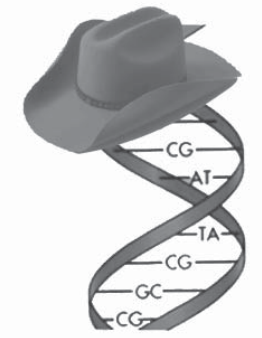
Photo by Evert Ruis

Dutch Cancer Society Muntendam prize, discussed the role of diet in VHL progression and postoperative recovery as well as the role of vitamins and other supplements. After lunch, Dr. Rachel Giles presented the Rare Disease Online Community for VHL and tried to place the Netherlands in a global VHL context. Patients, partners, youth (aged 12–25), and other interested supporters were then organized into four discussion groups supervised by prepared volunteers while snacks and drinks were served. It was a wonderful day!

Register now!

Can't wait to see you!

Details on page 16



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*Register for the Houston meeting**, 8:30 to 4 pm, Saturday, June 18:*

☐ One registration (includes lunch and breaks) @ $80 if booked by June 5 (or $100 thereafter) $_____

☐ Registration for two people (includes lunch and breaks) $150 before June 5 ($200 after) $_____

** Make your own Marriott Texas Medical Center Hotel for reservations, 713-796-0080, room per night: $99.00

☐ VHL Handbook, Kids' edition Supporters, $6.50 ea, List price $12.99 each $_____

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International members - please make payment by credit card if possible

Banking fees to process checks in non-US funds are now $35 per check.

Canadians, please send checks to: Canadian VHL Family Alliance, c/o Jill Shields, 4227 Hamilton Road, Dorchester, Ontario, N0L 1G0 Canada

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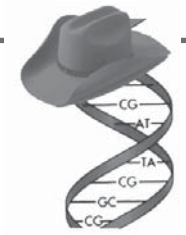
Please join us at one or more of the following events coming up!

see also vhl.org/meetings

REGISTER EARLY!

VHLFA National Family Conference

Saturday, June 18, 2011, Houston, Texas



Educate and Empower Yourself!

- **Dr. Scott McLean, DNA testing for VHL, and steps to your Genetic Health**
- **Dr. Eric Jonasch, Urologic Oncology, on the status of investigation toward a drug to help with VHL, including two new trials expected in 2011.**
- **Dr. Ian McCutcheon, Advances in treatment for hemangioblastomas**
- **Dr. H. Jeffrey Kim, Georgetown University Medical Center and NIH, Advances in diagnosis and treatment of Endolymphatic Sac Tumors (ELST)**
- **Advances in treatment for kidney tumors, including RFA, cryo, and robotic surgery -- strengths and limitations of each**
- **Advances in treatment of retinal tumors**
- **Evaluating and Monitoring Children with VHL**
- **Pheochromocytomas inside or outside the adrenals**
- **Nutrition and VHL -- keeping your immune system strong**
- **Coping and managing stress**

Latest info about clinical trials, ELST, pheos and more!

Sunday morning: Chapter Leaders' Meeting

Come join the team!

http://vhl.org/meetings/meet2011/

New York Regional Meeting

Saturday, June 16, 2011 (NEW DATE!) *Memorial Sloan Kettering*
For more information, visit http://vhl.org/meetings or contact us-ny@vhl.org

Dutch VHL Meeting (in Dutch/Flemish)

Saturday, Oct. 1, 2011 *in Bergen op Zoom* *For more information, contact info@vonhippellindau.nl*

10th International Medical Symposium on VHL

January 27-28, 2012, Houston, Texas **Invite your doctor! Continuing Medical Education Credits (CMEs) will be available** *For more information, visit vhl.org/conf2012* Hold the date! Plan to come!

Please check http://vhl.org/meetings for updates and directions or call the office, 800-767-4845, ext 4