

## Powerful Patient 2009, week 39

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### Dealing with Inconclusive DNA Testing

In making a diagnosis, DNA diagnostics are often considered the final arbiter of whether or not you have certain conditions. But what if the DNA testing is inconclusive? Three guests joined Joyce for a discussion of the practical and emotional turmoil this can create: Catherine Stolle, Ph.D., one of the top DNA testing units in the U.S.; Gayun Chan-Smutko, MSGC, of Massachusetts General Hospital; and Gary L. Wood, Psy.D., a clinical psychologist who understands first-hand the anxieties of having a genetic condition in the family.

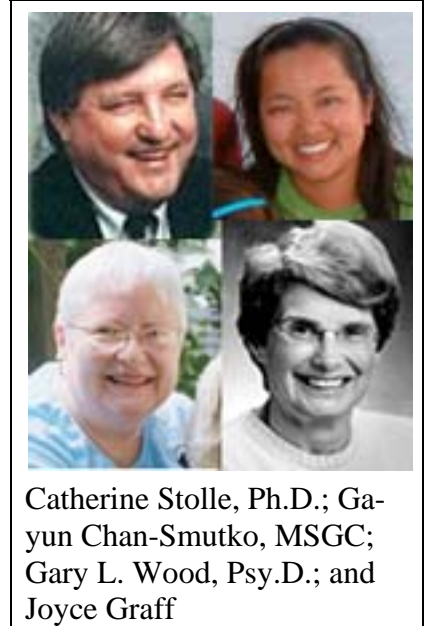
What happens when your DNA test comes back with a fuzzy answer? Where do we go from here?

VHL was described over 100 years ago. For 90 years the only way to diagnose VHL was through clinical criteria: if you have two or more different kinds of VHL-related tumors, or one kind of tumors and a first-degree relative with a diagnosis of VHL, then you have a clinical diagnosis of VHL.

Today there is a DNA test for VHL. The DNA test is now considered to be the conclusive way of determining whether someone has VHL. But there are a number of reasons why that test might in fact not be conclusive.

We talked about a fictional person with VHL, “Sam,” who has a hemangioblastoma and is talking with his neurosurgeon about whether or not it might be VHL. One option is for the neurosurgeon to order the test himself. The problem with that is that the test results, which are somewhat cryptic, come back to the ordering physician, and someone has to communicate them to the patient. The neurosurgeon is unlikely to be prepared to spend the time with the patient that it usually takes for the patient to understand and absorb the results. It’s not just a blood test like a cholesterol test with a relatively simple message for what you should do to treat it. It has far-reaching implications, not just for the current treatment, but for lifelong management for Sam, and potential implications for others in the family.

For these reasons it is strongly recommended that the patient be referred to a genetics professional who can discuss with the patient the family history, and potential implications for the family. Dr. Wood suggested that Sam visit a geneticist or genetic counselor and create a relationship with that professional so that even before the test there is a comfort level with the genetics professional that will help him hear and understand the results.



Catherine Stolle, Ph.D.; Gayun Chan-Smutko, MSGC; Gary L. Wood, Psy.D.; and Joyce Graff

Genetics professionals are trained in the ethics of having those discussions – training that other physicians may or may not have had. They also understand that this information does not always “take” the first time you hear it. As Ms. Chan said, it’s a bit like taking a drink from a fire hose. The patient should feel empowered to call again and ask again until they understand what it means to them.

Dr. Wood added that just knowing that it is okay to call again, gives the patient some feeling of control. It is much easier to understand difficult information when you are relaxed and not tense.

OK, so let’s say that “Sam” has multiple kinds of VHL tumors so we are pretty confident going into the DNA testing that he has a clinical diagnosis of VHL. But when the DNA test comes back, the results are inconclusive. What happens next?

Dr. Stolle said that she would review the case with the physician to make sure that the clinical findings are in fact consistent with VHL, and she would even do the test again to make sure that the lab did not make a mistake. It is important too to remember that not every DNA testing lab has a high “hit rate” – if, for example, their results are accurate 85% of the time, that means they are not accurate 15% of the time. So it would be important to look at the quality of the testing lab, and their relationship with a research team. Dr. Stolle’s lab has the highest “hit rate” for VHL, higher than 99%, and she works closely with the largest U.S. VHL research team.

For that reason, the VHL Family Alliance recommends that anyone who is the first person tested in their family should only go to a very high quality testing lab like Dr. Stolle’s lab. A “yes” answer from nearly any lab is likely a “yes,” but a “no” answer from a testing lab that has an 85% hit rate is really a “maybe” – there’s a 15% chance that it might in fact be a “yes.” In that case, it would be good to re-test at a more thorough lab.

Another possibility is mosaicism, which only occurs in the first person in a family to have VHL.

Jennifer called in to say that her family has clear clinical diagnoses of VHL for three generations, but very good labs have not been able to find the mutation. The testing was done in 2007. If the testing had been done before 2002, it would be worthwhile to try testing again. But a test done by a good lab in 2007 should be as accurate as it can be.

In Jennifer’s family they have been able to identify through linkage analysis that there is a common pattern in the gene that seems to be passed from one affected person to another, even though they can’t see the mutation.

Dr. Wood asked Jennifer how her family copes with this uncertainty. Her parents feel that people have children who pass away every day from horrible things you can’t predict. “We can’t live our lives in fear. Knowledge has helped us. My parents were adamant that my brother and I go to college and be able to provide a good living and insurance for our families just in case of health problems. And at least we know what to look out for to protect ourselves.”

Dr. Wood said that for himself, “I cope with living while VHL is happening. Life has uncertainties of its own, no matter what your genetic condition.”

At a certain point we have to admit that we still don’t understand everything there is to know about genetics. There are other ways that genes can be turned off. It might also be a change in a closely

related gene that causes much the same thing. It may be perfectly spelled, and still not be working correctly for some as yet unknown reason.

Ms. Chan said that we should view genetic testing as a tool which can be used to confirm a clinical suspicion. A negative or inconclusive test cannot rule out a diagnosis of VHL. It is important for the healthcare provider to explain to patients beforehand that genetic testing is not a perfect science. It is helpful to confirm a diagnosis, but when it's unclear, the best thing we can do is to screen the children to make sure that if they have VHL we will find any issues early and deal with them appropriately.

Dr. Wood said that he feels we should be looking for clarification, not certainty. We can often gain enough information to make reasonable estimations and offer advice, without achieving certainty. Almost no lab test is 100% certain. We get guidance, not certainty.

Joyce said that people will sometimes call and say, "They tell me this test is 99% accurate. How do I close that gap?" 99% is about as good as it gets in Nature. 85% I would worry about, but 99% I would not worry about.

Another two patients with clinical diagnoses of VHL have reported having a change in a place in the gene between the exons, in the area that used to be called "junk DNA", that has not been reported to be "causative of VHL". Ms. Chan spoke about the investigations she would do with such a patient to double-check the pathology, the clinical testing, and the family history, to make sure that it's VHL and not some very similar condition.

But at some point we have to simply say that the DNA testing is not going to bring us the clarity we had hoped for. Many people had children before there was DNA testing. All we knew was that each child was "at risk" for having VHL. With medical surveillance and watchfulness, we can still have some control in the situation. We can simply manage based on the clinical diagnosis of VHL.

Joyce manages uncertainty by making a list and making a plan. Dr. Wood added that not everyone can do that alone. They may be overwhelmed – the "victim" hijacks the thinking part of the brain. That's where a genetic counselor comes into play to help the person clarify their thinking. When we can't blame it on anything else, we often blame ourselves. He works with people to perform "blame-ectomies".

When we go for DNA diagnosis we are usually looking for guidance on three planes: current treatment, surveillance and management for the rest of this person's life, and the implications for the family.

Dr. Wood encourages families to talk with each other, and go toward each other. Having a disease like this can be very isolating, and the support of family and friends is extremely important. Subscribe to the podcast at <http://powerfulpatient.org>.

### **About our Guests:**

Gary L. Wood, Psy.D., is CEO of Wood & Associates, one of the leading

providers of Employee Assistance programs to corporations throughout the United States. See <http://www.woodassociates.net/> 800-343-4670

Catherine Stolle, Ph.D., FACMG, is head of the DNA testing laboratory at Children's Hospital of Philadelphia (CHOP), and co-author on a number of papers on DNA testing for VHL.

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<http://www.massgeneral.org/cancer/doctors/ccra.aspx> She serves as coordinator of the VHL Clinical Care Center at MGH.

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