Interview Transcript — Lindsay Middelton, R.N., C.G.C

I'm Jill Woodward. We're at the National Institutes of Health in Bethesda, Maryland and I'm here with Lindsay Middelton, who is a genetic counsellor with the National Cancer Institute. Lindsay, first off, can you tell us what is a genetic counsellor? What would be a typical day?

Being at NIH, my day is a little different than cancer counsellors around the country. When you see somebody, you need to prepare for that person. You need to make sure we have all the records in, did we get the imaging. Here at the NIH, we're a whole team and we've been studying BHD for fifteen years. I think we first saw a patient in 1998, so we get together several times a week: so we're in meetings a lot talking about the patients, talking about the research. So I attend those. At the NIH I also have regulatory responsibilities, research protocols, whereas counsellors on the outside of NIH spend a lot of their time interacting with insurance companies, getting pre-approval to do the genetic testing. And we don't do that here; I don't have to do that here.

And what genetic conditions do you work on?

We've been studying BHD since 1998. We've seen about 400 patients. I work with people with Von Hippel-Lindau, with hereditary papillary renal cancer, with HLRCC, with tuberous sclerosis. There's Cowden syndrome. There are a number.

So Lindsay, can you describe BHD mutation for us in lay terms?

I look at a gene like a recipe. So if the recipe has a mistake in it, the product does not work as well. The protein here in BHD is Folliculin. So if you have a mutation in the gene, the Folliculin that's produced by that BHD gene just doesn't work as well as it should. So that predisposes an individual to the development of one of three things that we know of today. Fibrofolliculomas; these are the face bumps, typically head and neck. So these are actual tumours, they're benign, involving a whole hair follicle. About 88% of people, perhaps, with BHD will have a fibrofolliculoma; some have one or two, others have many. It also predisposes to the development of lung cysts. About 80% of people who have BHD will have a lung cyst that you can visualise on a CAT scan. Everybody breathes just fine, we're not seeing lung

cancer, but those lung cysts predispose to the development of a pneumothorax. That's the medical term for the spontaneous collapse of a segment of a lung. We have three segments on one side, two on the other. And people with BHD who have a pneumothorax typically have one of their lobes go down—not life-threatening. The other aspect is a susceptibility to the development of multiple kidney tumours, in both kidneys. I believe it's 38% of our families have never had a kidney tumour, not one person has had one. But the majority of families have had somebody in their family who has had a kidney tumour, so it just predisposes the development of kidney tumours. As far as we know, that's the three things that we are aware of today.

So can you talk about how mutations in general occur or are inherited?

Mutations, genetic alterations or mutations, occur as a part of organic life. They happen to plants, they happen to animals, they happen to people. So in someone who has BHD, somebody in their family just spontaneously had a mutation in their gene. It's almost impossible to figure out why. We're all exposed to various mutagens in our world. We have ambient radiation in our air; we're exposed to thousands of chemicals so we really don't know. But once that spontaneous event happened, it doesn't go back and that's the way it transmitted down through the family.

So how is BHD transmitted?

Each offspring of a parent who has BHD has a fifty-fifty chance of inheriting that predisposing gene, BHD gene mutation, conferring just the susceptibility to these three things. It is transmitted vertically in a family, not brothers and sisters only. So it's dominant generation to generation.

What are the things that the patients that you've seen are most concerned about?

Well, I think what I hear a lot in people, is the concern that, especially if there are kidney tumours in the family, that their local doctors do not know anything about this, no one know anything about it. And they've never met anybody who has BHD. So it engenders a kind of a fear: what is this, no one knows about it, I'm worried about it. Then, another thing I hear most frequently of course is: how do I take care of myself, the person with BHD. I hear the

term kidney cancer is a scary term. Their doctors don't know how to handle it. Immediately after that is: what are the risks to my children. People are more worried about their children than themselves typically and they want to know about the risks, when should the children be tested, how can they talk to them.

So that brings me to the next question: should prospective parents be worried about passing this gene on to their offspring?

Well, you've used the word 'worry'. I think what most parents feel is guilt. I have worked with families with genetic conditions for 25, 30 years. I've tried my whole career to argue parents out of feeling guilt. It's nothing you did. You inherited probably from a parent. And so there's no need to feel guilt, you didn't do anything. But I've been taught by parents that I can't argue that guilt out. They've got it. We as parents tend to feel guilty about our kids and think if our kids do anything that we don't think is quite right we feel guilty. And then you add something that they literally pass down to their children that may be negative. You just can't argue that out. But I always ask parents: you probably got this from your parent, are you angry at your parent? I've never heard yes. I mean, it's difficult. And it's something that parents have to deal with, but I think it's the general feeling of guilt parents have.

So can you talk about how families, or how you recommend families get the BHD conversation started?

There's a communication style within families. Some families talk about everything, everybody knows everything and they talk all the time on the phone. Everybody knows who has what. No problem with those families. They'll have no problem with that. But there are other families that really don't communicate that well about health issues. At NIH we have people travelling in from all over the globe. Perfect opportunity to say why did you go to Bethesda, Maryland and get the conversation rolling. It's important that people understand that this is a very manageable condition. It's nothing that should shorten a lifespan. So I'd like people to at least have that kind of feeling before they talk to others, rather than scaring everybody in the family. I'd like people to have a fairly good understanding about BHD before they start talking to family members.

Talk about any possible risks that there might be for patients to get genetic testing here in the United States, where insurance companies have the concept of pre-existing condition.

The GINA act, G-I-N-A act of 2008 that President Bush signed, has provisions in there that someone who has a gene that doesn't work, has a genetic alteration, that they cannot be considered as having a pre-existing condition. But I don't have that expertise to interpret the language in a regulatory law. But I did see there is a provision about pre-existing conditions. And actually the act can be accessed easily by googling GINA.

In all of your years working on BHD, what has been one of the most surprising or exciting research findings?

For me personally, as a genetic person, last summer we identified in our lab downstairs a type of mutation in the BHD gene that had not been identified, it's called a deletion. And that increased the detection rate. When you have genetic testing of the first individual in a family, it's never a 100% chance you will find that mutation. So last summer, finding a different type of mutation was very exciting to me. And we have now found a number of people with BHD have that type of mutation. And to me that just increases the detection rate. I think it's very important in families to know the mutation because then everybody can be tested. And those who have the mutation can just have their kidneys screened. So I'm always interested in increasing detection rates. So I was excited about that. I think the other thing that I found exciting was that early on in research, we knew that kidney tumours were associated with this gene. There are many types of kidney tumours and they all act differently. Some are more aggressive, some are more likely than others to leave the kidney than others and metastasise. So it was exciting to us, not just to me, us here to find that the types of kidney tumours associated with BHD tend to be the less aggressive, slow growing type. And that was exciting to me in the world of BHD.

With your unique perspective as a genetic counsellor, what do you think would be the greatest area of research needed in BHD?

We have been working hard in our laboratories and clinically, to understand BHD, to understand the pathways, the biochemical and molecular pathways involved with this

condition—why do people get tumours. And I think the ultimate goal that we're striving for, is to find a clinical trial, an agent that will be effective certainly with kidney tumours. And we're very close to that here.

And by agent, do you mean drug?

Drug. A drug therapeutic trial. A drug to give people as an option, those who have kidney tumours. Might we be able to shrink those tumours? That would be wonderful. Would this agent, this drug agent, help with their fibrofolliculomas, with their lung cysts? We don't know. We're really working hard for that. We're getting very close here at NIH to have a clinical trial.

So is there anything else besides a drug that you think is very important for research right now?

Yes. What I have heard recently from patients is the need to increase research in the lung. Why do lung cysts develop? How do they predispose to pneumothorax? I've heard that resoundingly, certainly from the patients in Europe and more recently here. There's just not enough pulmonologists and thoracic surgeons who are knowledgeable and who have worked with patients with BHD. That would be a big area of research I think that's needed.

You were at the Third BHD symposium in Maastricht. What did you find most interesting or exciting at the Symposium?

When you work with people with rare diseases, every paper, every presentation, they're all pieces of a puzzle, they're all significant. For me personally, because I just heard from patients and I realised we do not know enough about the pathophysiology of lungs in BHD. I was very excited to hear Dr Scott and Dr Seyama, their work on basic science of what's going on in the lung. And that was very exciting for me to hear that there were pulmonologists working on this.

The other presentation I was most interested in was from Richard Harbottle's group in the United Kingdom. He's working with a novel approach to gene therapy. He's using non-viral

vectors as a delivery model perhaps in BHD for gene therapy. It's very new, we don't know where it's going but I think it's very exciting.

You led the patient and families sessions at the Third BHD Symposium; what was beneficial for everyone involved?

I always enjoy talking to patients, for me personally it was satisfying. But more importantly, so many patients with BHD have never seen another person with BHD. So for them to talk to one another, it's very exciting, it's like an 'aha' moment. This happened last year at the second international meeting. I was prepared to lead the session; all I had to do was say one question and everybody started talking. It was just so wonderful to see how empowering it was for everybody to gain knowledge from one another. People with BHD are going to learn more about BHD from one other than from us. And to allow patients to actually talk to the researchers, it's very exciting and I think that happened there. I loved it; it was wonderful. More of that!