LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Patient-Doctor Perspectives: Hereditary Myelodysplastic Syndromes (MDS)'

Description:

Join us as we start a brand new series, *Patient-Doctor Perspectives*, where we explore a diagnosis from the view of a patient and doctor. In this episode, we speak to Ashley Cámara, a Myelodysplastic Syndromes (MDS) survivor and advocate and Dr. Lucy Godley from The University of Chicago Medicine. Ashley shares her story of having two MDS diagnoses in her family – first her brother and then herself. Dr. Godley then delves deeper into inherited myeloid malignancies and how genetic links may lead to preventative treatment options.

Transcript:

Elissa: Welcome to *The Bloodline with LLS*. I'm Elissa.

Edith: I'm Edith.

Lizette: And I'm Lizette. Thank you so much for joining us on this episode.

Elissa: Today we will be speaking with Ashley Cámara and Dr. Lucy Godley. Ashley is a survivor of myelodysplastic syndrome, also known as MDS, who was diagnosed less than two years after her brother had passed away from the same disease. Following a stem cell transplant that resulted in complete remission, Ashley has become an advocate for MDS patients and young adults with cancer and has recently started her master's degree in social work. With the unique circumstances surrounding the similar diagnoses of siblings, she was treated by and worked closely with Dr. Godley and her team to determine her genetic predisposition to MDS.

Dr. Lucy Godley is a physician scientist with clinic, research, and faculty responsibilities at The University of Chicago. She seeks to understand disease on a molecular basis and has been able to bring that perspective of care to her patients. Dr. Godley is the

co-chair of the Myeloid Malignancy Variant Curation Expert Panel which was created to perform gene and disease-specific modifications for inherited myeloid malignancies.

In this episode, we will be discussing hereditary MDS, genetic links, and the treatments and protocols for these inherited malignancies. Welcome Ashley and Dr. Godley.

Ashley Cámara: Hi, thank you for having me.

Dr. Lucy Godley: Thank you.

Elissa: So, before we get into today's topic of hereditary MDS, we would like to know a little bit about our speakers. We'll start with Dr. Godley. How did you get into the field of medicine, and what brought you to studying inherited myeloid malignancies?

Dr. Godley: Thank you. I've been interested in cancer biology ever since I was a child really. I grew up in New Haven, Connecticut, and I started working in a laboratory when I was 16 in high school. And I loved the science, I loved the inquiry and the discovery, and so I've pursued that through my whole career.

I became interested in inherited predisposition to blood cancers from my patients. When I started talking to my patients and taking their personal and family histories, I was struck by how many of them have multiple cancers themselves or multiple cancers in close relatives. And I began testing my families and my patients for these types of diseases and started diagnosing them, and this snowballed and grew into a very deep interest in genetic predisposition, which I think is much, much more common than what was taught to me when I was in my training.

Lizette: Sure, we don't hear as much with blood cancers for genetic predisposition, so this is very interesting.

Dr. Godley: I think the lay public knows about BRCA1 and 2 mutations, for example, and they would say, "Oh, we know, you know, those predisposed to breast and ovarian cancer." But I think they're much less likely to understand that those are also Fanconi

anemia genes. They're essential for bone marrow function, and they also predispose to bone marrow-derived cancers. So, I think we need to do a lot to educate the lay public on these disorders. They are much, much more common than what people think.

Elissa: Very interesting.

Lizette: Yeah, definitely. And, Dr. Godley, can you tell us what exactly is myelodysplastic syndromes, MDS?

Dr. Godley: Sure. Myelodysplastic syndrome is actually an umbrella term. We have several distinct diseases that we put under that umbrella. It's essentially a condition of bone marrow failure where the bone marrow is not able to produce its normal cells. And so, typically, people have low blood counts out in their peripheral blood; that's how they're detected, and the bone marrows can sometimes have too many cells in the bone marrow that never make it out into the blood, or the bone marrows can actually be pretty empty. But in all cases, there is deficiency of effective cells out in the peripheral blood.

Lizette: Thanks. And I know that we're going to speak with Ashley in regards to her MDS. Is it rare to have an inherited type of MDS?

Dr. Godley: You know, that's an excellent question. We actually don't know the frequency of inherited predisposition mutations across all patients who get MDS. MDS is typically diagnosed in older people, so the average age of diagnosis of MDS in the United States is 68 to 70. So, it is unusual for a very young person to get myelodysplastic syndrome. Pediatricians and our groups and others have been very interested in answering the question of why should a young person get myelodysplastic syndrome? And depending on what age you present with MDS, you can have upwards of 25% chance of having an inherited predisposing mutation.

That doesn't mean that people who present in a normal age range, around, you know, 65-75 years old, can't have germline predisposition. In fact, they can. We know that germline DDX41 mutations give rise to MDS in the same age range as the general population. What we don't know, as I said before, is what's the frequency of germline mutations across the entire age spectrum, and that's a question we'd really like to answer soon.

Lizette: Sure, and I know it was really interesting because, Ashley, you look very young. I don't know your age, but I do know that you are quite young for MDS, as well as your brother was quite young when he was diagnosed.

Ashley: Correct, yes.

Elissa: Ashley, so you were diagnosed with MDS, but years prior to that, your brother was diagnosed with the same disease. Can you tell us about your family's life leading up to and after your brother's diagnosis?

Ashley: So, my brother and I were born in Mexico and we were the typical siblings that would fight and have great moments. And we were super healthy. Probably would only get sick of a cold maybe once or twice a year. And when my brother got sick, he was diagnosed in 2013. He was 23 years old. It was very weird because we had no idea what was happening. The symptoms that he was presenting, at first, we didn't think anything of cancer. We thought it was maybe hepatitis because of the symptoms, right?

So, he went to get a blood test and the doctor there called us right away, a few hours after that. And they told us, "You know what, you need to take your brother to the emergency room because he does not have any blood counts high, no red cells, no white cells, nothing." So, we rushed him to the emergency room; and, you know, they did different tests, and they diagnosed him with myelodysplastic syndrome.

So, after that, he started treatment; and he was doing well after a couple of months. And he definitely needed a stem cell transplant, but the doctor in Mexico was trying to keep him stable prior to that. So, he was fine for a couple months, and then he was ready to get a stem cell transplant; and when he went into transplant, his MDS developed into an AML, which is an acute myeloid leukemia. It's aggressive. So, when he went into transplant, unfortunately, because of complications of the transplant, he passed away.

So then, after his passing in 2015, I was in college. I was going to actually start my last semester of college, and I was in the United States. I was here in Chicago with my family, and I was on my way to return back to Mexico for that last semester of college when I started presenting symptoms – different symptoms than my brother's – and we didn't know what was happening.

One of my main symptoms was that my feet were hurting really bad, and I wasn't able to walk. So, my mom had to rush me to the emergency room, and I saw my brother's doctor there and he started doing some studies. And they were talking about maybe it was lupus, maybe it was something different. It really didn't cross their mind that, you know, it could be MDS again because it's unusual, like Dr. Godley mentioned.

So, the last test was a bone marrow biopsy. And a couple of weeks later, I was diagnosed with MDS.

Elissa: So, what was that like for you and your family after this second diagnosis within the family of MDS?

Ashley: At first, it was very shocking because I remember when I asked him if I needed to get tested every couple of months or maybe every year because of my brother's diagnosis. And I remember him telling me, "You know, this is unusual." He's like, "I don't think you need to; it would be really up to you if you would want to do it." So, I said, "Okay." And all of a sudden, I get diagnosed.

So I think it was a shock for everybody, even the doctor, because this is very rare and unusual. But I guess we knew what we needed to do; and we just started treatment and everything else.

Elissa: So how did you get in contact with Dr. Godley and ended up at The University of Chicago for your treatment?

Ashley: So, we got connected because we asked our doctor in Mexico that we wanted to continue treatment, but we wanted to do it in the United States. So, he actually reached out to one of his colleagues, Dr. Guillermo Garcia-Manero at MD Anderson; and that was the first referral that we had. But my mom wanted us to come to Chicago. So, Dr. Garcia-Manero was the one that referred us to Dr. Lucy Godley, and then my mom reached out to Dr. Godley and we just came to Chicago.

Edith: Dr. Godley, when you hear from families who are dealing with these unique circumstances of having more than one family member diagnosed with the same blood cancer, what are the next steps for you?

Dr. Godley: So, when I hear from families or doctors who have families with multiple cases of blood cancers, the first question is how can we get appropriate testing for the affected individuals? And this is difficult because appropriate testing, unfortunately, is not available across all commercial and academic laboratories in the United States. So, the first hurdle is to help people get appropriate comprehensive testing for all of the different germline predisposition syndromes.

And part of what makes this difficult is that we are identifying more and more syndromes every day, and so the platforms that are used to test for these syndromes, they have to be nimble. They have to be able to expand and accommodate a very rapid increase in learning about these different syndromes.

Also, the mutation types that we see are varied, and so the platforms that are used for testing need to cover all those different mutation types. They have to be able to detect them. And that is really quite challenging.

It's also really difficult for patients and referring doctors to know which tests are comprehensive. We actually just published a paper a few months ago comparing the different academic and commercial testing platforms for inherited predisposition in this space. And it's shocking how little overlap there is in these different platforms and so essentially how patchy the testing is.

And so even if a patient or a doctor gets a report back that's negative, you really have to look very closely to see what was tested, what genes were tested, what coverage of the genes, and what types of mutations could be detected because we've seen many cases where someone gets a negative test, but the test wasn't comprehensive.

So, the first step for me is getting appropriate clinical testing for people, and then if there's a positive test result, explaining that result to patients and families and then offering cascade testing throughout the family and appropriate treatment and surveillance strategies for that individual.

Edith: Ashley, what type of transplant did you have?

Ashley: So for my treatment, I had to receive a stem cell transplant, same as my brother. So, I had five days of chemo, three different types of chemo, and two days' rest, and then I had my stem cell transplant. It was an allogeneic stem cell transplant.

Elissa: What was the process like after your transplant? Did you have much treatment afterwards or just kind of regular testing and blood tests?

Ashley: So, after transplant, I had to see the doctors very often. I started with three times a week, and then it kind of went slowly, making some gaps. And I was able to go two and then ones and then every month. And now, luckily, I'm able to see Dr.

Godley every six months, so far. So I'm hoping that soon it'll be a year. But, yeah, I would have to go to the hospital very often after it for checkups.

Elissa: As you were going through your treatment and diagnostic test, did they find a genetic link that gave you a predisposition to MDS?

Ashley: So, yes. After testing, they did find out about a link. It was a mutation in one of my genes. So, they were able to look into my genes, some family members; and, yes, they were able to find a link.

Edith: Dr. Godley, when you find these genetic mutations, is the treatment protocol different than the standard for MDS?

Dr. Godley: That's a great question. Generally speaking, the treatment of someone's bone marrow cancer initially is not different. Typically, we treat the presenting disease, in this case myelodysplastic syndrome, with standard therapy. And Ashley first received standard therapy prior to her stem cell transplant.

At the time of stem cell transplant though, we have to be very careful with people who have inherited predisposing mutations for two reasons. First of all, depending on the gene, some of them predispose to severe toxicity with high doses of chemotherapy. And since we use high doses of chemotherapy in some transplant regimens, we sometimes have to adjust the dose of chemotherapy at the time of transplant to avoid that severe toxicity.

The second thing is many patients having stem cell transplants have that transplant from cells taken from a relative. And if these mutations are inherited in the family, that means potential donors can have these mutations as well. And we really don't want to use stem cells that come from those mutated donors for a couple of reasons.

First, when we ask a donor to give stem cells, we generally give them a growth factor for their bone marrow. And if that individual already has a predisposition to leukemia,

when we give them a bone marrow stimulant like that growth factor, we worry that we can induce or accelerate the development of leukemia in the donor.

And, secondly, some of these mutations are in master regulators or controllers of stem cell function. And if they have a mutation in one of those genes, those stem cells don't work very well. And so, when you ask those stem cells to go into the new person, into the initial patient, the recipient, and set up a new bone marrow, they have a lot of trouble. And so those recipients don't do very well.

We know that this is true for people who have inherited mutations of the gene called RUNX1 or CEBP-alpha. But we know of many, many, many different inherited predisposition genes. And we don't know what happens if we use donor cells from those individuals. So, there's a lot of information that we need to gather from research to understand if there are some mutations that are actually permissive or, you know, have no problem when we use them in transplant.

In general, we are nervous to use stem cells that have one of these master regulator mutations because of what has been seen anecdotally in individuals and families who were not recognized to have these conditions when transplant was done.

Lizette: And like you said, you know, most of us have not heard about all of these different hereditary or genetic links to blood cancers. You mentioned breast cancer. You mentioned other cancers. And I feel like since there's not so many young patients that have MDS, and in this situation, I just want to make sure that patients that go in, is it important to really tell the doctors that somebody else in your family had a certain diagnosis? Even if you're not sure?

Dr. Godley: Yes, absolutely. So being very candid with doctors about your personal family history is very important.

But the other thing that's important is that our knowledge is really changing, and people around the world are really listening; and they're very much attuned now to this idea that inherited predisposition is more common than what we thought.

And so now because of the literature that exists in the pediatric age group, which is say from 0 to 25, 30 years old and other data that will come out soon in young adults, say from 18 to 40 years old, anyone diagnosed with MDS under 40, 45 years old, most doctors, I think now, will think about inherited predisposition. The difficulty will be how do they access that testing.

And what we see very commonly is that patients and families are worried about their DNA. Like Ashley talked about talking with her doctor after her brother was diagnosed and asking the doctor, "Well, should I be worried?" You know, and it's often the doctors and the healthcare workers who say, "No, no, and blood cancers aren't inherited." That is changing though, as people are coming to recognize that these inherited predispositions are more common, more and more doctors are understanding the importance of that personal and family history.

Lizette: That's good to know because throughout the years, that's what we've always been told too, that there's such a low chance that, your family members will be okay. But that question comes up on all of our education programs, on all our webcasts, our podcasts.

Dr. Godley: Yeah, and the thing that I think is going to be true is that each individual syndrome, if you will, say RUNX1 or GATA2 or CEBP-alpha or TERT or TERC, each one may be relatively rare. But there are so many that in total, this phenomenon is common. And I think that's going to be something that people are going to need to think about a little bit.

So, people are always saying, "Oh, well, inherited RUNX1 mutations are rare. Inherited CEBP-alpha mutations are rare. Inherited this is rare." But you go on and on and on and on and on, and the list is 75 genes. It's not rare anymore.

Lizette: Right.

Elissa: So, do you think we'll get to a point like they do with the BRCA gene and in testing children of blood cancer patients?

Dr. Godley: Well, we already test children clinically when it's appropriate. Some of these predisposition syndromes can present in childhood, like, you know, Ashley was a young adult. And there are children who present, we were hearing in our meeting today, at birth with leukemia or very soon after birth or they present at five years old. If we identify the mutation in the parent, you know, the question comes up, "Should we do testing in the children?" And it very much depends on which gene is mutated and whether that child would be at risk for disease in a pediatric age group or not. So I can't really answer the question. Generally, it's a very specific answer.

I thought you were going to ask when will the day be that we do germline or inherited mutation testing on everyone who walks in the door or on every potential bone marrow donor who's a relative or even who's not a relative. You know, we have unrelated donors. They have inherited variants or cord cells that are used in transplant.

And I think you won't be surprised to hear that I do advocate a future that is going to come very soon where we are going to do much, much more inherited predisposition testing. And I wouldn't be surprised if in the next five to ten years doing this kind of inherited, what we call a germline or inherited mutation testing is standard at the time of presentation for anyone of any blood cancer of any age.

Elissa: If you did find an inherited gene, I mean would there be anything to do at that point? Or is it just kind of, okay, I've got this gene. I know that there is a much greater chance that I could get a blood cancer.

Dr. Godley: Right, so you're asking a very important question. So, if we know that an individual has an inherited mutation, what can we do when they're in the healthy state?

This is an excellent question. And depending on the gene mutation, there are a few different options. The first one is, say for patients with an inherited mutation in the gene called CEBP-alpha. Those individuals who have a mutation, especially at the beginning of the gene, they have a very high- we use the term penetrance - of developing a malignancy, meaning that they are destined to get leukemia in the future. And so ethicists have argued that in that situation, if you know that someone is destined to get a leukemia, why would you wait to let them get that leukemia when you could transplant them and cure them?

This particular syndrome only predisposes, as far as we know, to bone marrow cancer. So, if you do a preemptive allogeneic stem cell transplant, you take away the entire risk of that mutation.

Elissa: But then there's a risk of the transplant in itself for GVHD and-.

Dr. Godley: Correct. That is correct. Transplant is not without risk. So, if you were a parent of a five-year-old and you knew that child was going to develop leukemia in the next several years, would you decide to do a preemptive transplant or would you wait, watch that person very carefully? These are the discussions that happen between parents and doctors or patients and doctors. Do I want to watch and wait and, you know, watch myself very closely, or do I want to have a preemptive stem cell transplant?

In the case of CEBP-alpha mutations, one can make a very strong argument for preemptive transplant, just because of the very high penetrance that almost everyone is destined to get leukemia.

For all of the other syndromes, we really don't know who's going to go on to get a bone marrow cancer. And in particular, in families where everyone has the same mutation, not everybody gets disease. So what's making some people get leukemia and others not?

What we advocate is watching people very, very closely. And what does watching mean? It means doing a baseline bone marrow biopsy and seeing what their bone marrow looks like when their blood counts are pretty normal; watching their blood counts very carefully over time, that means three or four times a year; potentially doing annual or yearly bone marrow biopsies or at least bone marrow biopsies when those blood counts change.

Also, some of these gene mutations, remember they have risk to other organs. So doing careful surveillance of other organs to maintain, you know, good organ function. We know that some of these gene mutations predispose to solid tumors, and people should have surveillance like colonoscopies or mammograms or breast MRIs earlier and more frequently than the general population.

So what we do is we develop a surveillance plan for each patient, and we disseminate this plan or these ideas throughout the family, teach other doctors so that people can take a very proactive stance to their condition and monitor themselves very carefully.

What's the future? The future is doing research to understand what's driving the progression of leukemia and then intervening to delay or even prevent leukemia in these individuals.

Elissa: That's really interesting. So, going back to Ashley - you're now a few years out of your stem cell transplant; and you've since become an advocate for young adults with cancer and also started working towards a social work degree. I would love to hear how that all transpired.

Ashley: So, yes, I am three years post-transplant; and actually, advocacy for me, it started when I started sharing my story. I shared my story for the Illinois Medical District Guest House in Chicago that offered me housing for after treatment when I was in the hospital. After my few days in the -hospital after transplant, I was able to stay there just in case of emergencies. you have to be like a certain amount of distance between the hospital and your home, so they were able to house me; and so I shared my story for them first. And then I started sharing it for other organizations, including The University of Chicago Medicine.

I also realized that MDS, it's really rare for young adults. Everything that I've learned through my brother's treatment and my treatment, and like Dr. Godley mentioned before, this is a disease that it's usually in older adults, 68+. So, the fact that it can happen to young adults like it happened with me and my brother, that kind of sparked the interest too of making aware of how important it is to know that this can happen to young adults as well.

Elissa: Young adults in a family at that.

Ashley: Correct, yeah. And in regards to social work, I just had a great experience with my social worker at The University of Chicago Medicine. Shoutout to Mark if he's listening to this. But he was just great, and I have a lot of friends, too, that work in the field that, honestly, just, you know, have inspired me to do the same work.

And basically, that's what I want to do. I still don't know what field specifically, like in the hospital or in the school. But it's something that I want to do. I want to help, help others like I was helped as well.

Elissa: That's great. That's a great kind of, you know, continuation of your cancer journey and your story. I love it.

Ashley: Thank you.

Edith: On our patient podcast homepage, we have a quote that says, "After a diagnosis comes hope. Based on your cancer journey and advocacy, Ashley, what word would you choose to complete that sentence? After a diagnosis comes-"

Ashley: Wow, that's a great quote. I would say life. You know, because after being diagnosed and being through everything and thinking that you may not get out of it; and, you know, after the experience I had with my brother, I thought like, you know, after a diagnosis, there is life. And, you know, I'm here living.

Edith: So strong.

Ashley: And enjoying so. Yeah.

Edith: And you will be.

Ashley: Thank you.

Elissa: Now regarding hope, a question to you, Dr. Godley. With the identification of genetic links and the continued research on hereditary MDS, what would you say to patients and their families to give them hope after a diagnosis of an inherited malignancy?

Dr. Godley: I think the diagnosis of an inherited malignancy gives power to people. A lot of these patients and families look at their family trees and their histories, and they feel like there's something in my DNA. That's what one of the patients told her local doctor. There's something in my DNA. Just look at, look at all these people.

I diagnosed someone on the East Coast who had been going to a major medical center for 13 years, and he and many of his relatives had acute myeloid leukemia. And I talked to him on the phone, and within a few minutes I could predict which gene mutation he had just from the characteristics of who had been diagnosed in the family and at what age.

And after having been treated for almost 15 years and wondering "what's in my family, why did all these people get this," we were able to test him and find out. And then we were able to show that his children actually had not inherited the mutation. And so all that worry that had gone into all these years as he watched his children grow and wonder, are my children going to have whatever it is that I have? We were able to take all that worry away.

And for people who test positive, I think it's power because rather than worry all the time, you can take very active surveillance and, we can detect a lot from the peripheral blood and a lot from bone marrow biopsies; and we should be able to identify the progression very early, well before somebody has full blown acute leukemia with all the complications that that brings.

And we do have transplants, and transplants are getting better and better all the time. And so I think there's a lot of hope in knowing. I think there's a lot of power in knowing what's causing people's diseases. And I think the future with more research is only going to make people's lives be able to be lived with less and less worry and fewer and fewer complications. And so a better and better quality of life with time.

Elissa: The future of research definitely provides hope to so many people. It's all thanks to people just like you that are, continuing your research on these inherited malignancies and other blood cancers. And we certainly appreciate it and providing all this hope to patients.

Dr. Godley: Well, thank you, but we couldn't do our work without the patients, right? And the patients and the families remain so engaged in our work. We've had many families that have been involved in research that have identified new predisposition syndromes that have come to visit the lab. You know, they want to see where the work is done. And so people get very, very engaged; and they take a lot of pride in participating in the process of research that allows the whole world's knowledge to increase; and that makes things better for the next generation of patients and families.

And I also want to thank The LLS and other foundations for funding work on inherited predisposition because when I first had this idea that inherited predisposition was much more common than what I was taught, major funding agencies like federal funding agencies, they have a harder time funding ideas that are not well-accepted. And so it's really, really important to have foundations like LLS to do that cutting edge research and to provide the patient advocacy that you do. So thank you for everything that you do.

Elissa: Thank you, Ashley and Dr. Godley so much. Ashley, I know it's sometimes hard to share your story as a patient and a survivor. And Dr. Godley, thank you for sharing your expertise with us; and our listeners, we appreciate you and we know that our listeners are very appreciative of hearing all about hereditary malignancies as it is fairly rare and unknown. So we are so happy to have you today.

Ashley: Thank you. Thank you for having us.

Dr. Godley: Thanks very much.

Elissa: And thank you to everyone listening today. *The Bloodline with LLS* is one part of the mission of the Leukemia & Lymphoma Society to improve the quality of lives of patients and their families. To help us continue to provide the engaging content for all people affected by cancer, we would like to ask you to complete a brief survey that can be found in the show notes. This is your opportunity to provide feedback and suggested topics that will help so many people.

We would also like to know about you and how we can serve you better. The survey's completely anonymous and no identifying information will be taken. We hope this podcast helped you today. Stay tuned for more information on the resources that LLS has for you or your loved ones who have been affected by cancer.

Have you or a loved one been affected by a blood cancer? LLS has many resources available to you – financial support, peer-to-peer connection, nutritional support, and

more. We encourage patients and caregivers to contact our information specialists at 1-800-955-4572 or go to LLS.org/PatientSupport. You can also find information specific to young adults at LLS.org/YoungAdults. All of these links will be found in the show notes or at thebloodline.org.

If you have further questions for Dr. Lucy Godley, she can be reached by email at lgodley@medicine.bsd.uchicago.edu. This email will also be found in the show notes.

Thank you for listening. Be sure to subscribe to *The Bloodline* so you don't miss an episode. We look forward to having you join us next time.