



WINN FELINE FOUNDATION

For the Health and Well-being of All Cats

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2012 WINN FELINE FOUNDATION SYMPOSIUM TRANSCRIPT

Dr. Leslie Lyons: Next Generation of Genetics

Introduction

Steve Dale: Hello, welcome, good afternoon. Welcome to the Winn Feline Foundation Symposium. Do you all like cats? Do you all love cats? That's better. We are going to hear a whole lot about two very important topics. We have amazing speakers. The Winn Feline Foundation Symposium has been going on for several decades now, and we do get the best people in the country. Today you are about to hear two of the best in the country. I am here with one of the best in the country to my right, your left, Dr. Susan Little, who speaks all over the world. Before we start, we are going to tell you a little bit about the Winn Feline Foundation.

Before we do that, index cards like this, they are right there at your tables in front of you, at least they should be. Fill them out if you have questions. Then, at the end, what you are going to do is hand the index cards to the captain of the table. Then, this lady right here, Maureen Walsh of the Winn Feline Foundation, will walk around, pick up the index cards and give them to me, and I will read questions and we will answer as many as we have time for. For the veterinarians that are here looking for continuing education credit, you have come to the right place, but, you have to fill out the evaluation forms that are at the table right in front of you, and then where you registered, where you came in, where those two lovely ladies said "welcome", that is who you give those to. Then they can give you what you need to get your continuing education credit. When we start, please have cellphones completely turned down or on vibrate or off, because we don't want to disturb other people.

I also have another announcement to make. About this time last year, the Winn Feline Foundation Symposium was on something horrible called feline infectious peritonitis. You are going to hear about cardiomyopathy and two of Winn's many initiatives are to some way, certainly somehow, and well within my lifetime, I'm young, we are going to solve these problems. She is looking at me like "you are really not young" that lady over there. Don't know why that is. Today, we just got a check for \$10,000 to the Bria fund for FIP research.

So we are going to tell you a little bit about the Winn Feline Foundation; Susan Little is going to do that. By the way, if you haven't checked this out and you want to know everything and I do mean *everything* there is to know about cats, or instead of joining a health club, because her book, which is 1400 pages long, 1400 pages, it is this big; carrying it around, you work off calories. The name of the book is The Cat: Clinical Medicine and Management. Dr. Susan Little here to tell you a little bit better about who we are.

Dr. Susan Little: Thank you very much Steve. So it is a joy for me to get to work with Steve because I look at it as beauty and the beast. I don't know about you guys, but that is the way I look at it. Of course he is the beauty; I get to be the beast.

Steve Dale: I don't think so.

Dr. Susan Little: After a margarita or two, yup.

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Steve Dale: No, no, no, no.

Dr. Susan Little: Okay, so my job this afternoon is to talk to you a little bit, for those of you in the room who may not know very much about the Winn Feline Foundation yet, I will tell you a little bit about us. So, we are a non-profit organization. We have been in existence since 1968. Some of you may remember our 40th anniversary celebration a few years ago, which was a big milestone for us. So our primary focus, our only focus, is to fund feline medical research because no other organization in the world funds only Feline Medical Research and unfortunately still at this time, despite the fact that cats are the number 1 pet in North America, they receive only a tiny percentage of the research funding that is out there. The dog world gets more than we do, and you know, that just shouldn't be. Should it? It just shouldn't be. So, one of our goals of course is to provide more funding through your generous donations and through our cooperation with some of our corporate partners, to enable researchers, like people you are going to hear speak tonight, to advance feline health and welfare. That helps you and I as pet owners. It helps us as veterinarians. It helps everybody who has a stake in the future of the pets that we love so much. So many of you will know about the important advancements that Winn has been able to help fund or be a part of over the years. So some things like knowing that cats have blood groups and knowing how important that is in veterinary medicine and in transfusion medicine; and for some of you with certain breeds, for breeding your cats that is important. The role that taurine played in virtually eradicating an important cardiomyopathy. You know, we should be so lucky we can eradicate hypertrophic cardiomyopathy. Well, Winn played a role in helping fund the research that eliminated, or virtually eliminated dilated cardiomyopathy. All other kinds of things you can see on that slide; measuring blood pressure, polycystic kidney disease through the work of Dr. Lyons, learning how to give oral medication safely to cats so that it does not cause esophageal disease, treating diabetes, things that touch all of us, whether you are breeder or you are just a cat owner or you are a cat lover, it touches all of us. So our role has been deep I think, and our goal is to continue this and push this into the future and continue to make the advancements that we all need. So we have still so much work to do. As proud as I am of what is on that slide, we have so much more work to do and we are going to do it with your help, I know. So thank you for being here and thank you for supporting us. Steve is going to talk to you about one of our really important funds, which is the topic of our discussion here tonight.

Steve Dale: Thank you. So, there I was just one day sitting in my office and my wife comes up to me and says "Steve, we've got to do something about our dog, Lucy." She did animal assisted therapy. You know what that is? Where you go, in this case Lucy went to the rehab institute of Chicago, a very famous place, and both children and adults benefited by our little dog. One of the things our little dog, Lucy, did was tricks. She wanted a new one. So I thought "what am I going to teach Lucy?" I don't know why, but I thought it would be fun if Lucy could play a little kids piano. Does that sound kind of fun? What made me think of that? So I got a little kid's piano and began the process of clicker training. So I clicked and gave Lucy the dog a treat, and click and treat, click and treat, and Lucy began, as I began to sort of mold the behavior, and the paw would lift up a little bit, and then lift a little bit more, and a little bit more and I was going through, and Lucy was learning, it was going fine. Then I closed the door to this room that we were working in. I didn't close it all the way and in walked that cat Ricky. Ricky, who is a Devon Rex cat, looked at me, looked at the dog and then went "ping" on the piano. I thought "what I am fooling around with this dog for?"

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Ricky was a very social cat anyway, and I have always wanted to demonstrate that pretty much anything you can teach a dog to do, you can teach a cat to do, except the cat may do it better, and I wanted to go out and show the world this. Now, this was before the days of You Tube. The internet was around, but you weren't showing videos, but I will tell you, Ricky did more television than I did. People would come over with the TV cameras and Ricky learned, "oh my gosh I'm going to get treats probably and I will get attention" and actually then when the camera light, the little red light you would see on a TV camera, a real TV camera, he would perform. I mean do all these things, and he did more than just play the piano. He also could jump through a hula hoop if you happened to have one, or if you had a little kid, he would jump over the kid. If you had a dog that could do a down stay, he would jump over the dog. If you had a series of dogs, he could jump over the series of dogs, and then he could do this; come when called. Ricky was amazing. Have any of you ever had a cat that just somehow, or a dog that you had this pet, that you had a relationship with that was hard to even define? And you wonder in your lifetime if you are ever going to have that again. You know what I am talking about? I mean I swear, if I fell down a well, the cat would be there to get the police and bring the police to the well to rescue me like Timmy and Lassie. He was amazing, and he knew what I was thinking, and I kind of knew what he was thinking. Training him to do another trick was easy.

Then one day I brought him to the veterinary clinic because my veterinarian complained to me that "We have never had a piano recital here at our clinic, why don't you do it here?" So we did, and everybody you know, applauded as Ricky played the piano and all that. We would go to Pet Stores like Pet Smart and Petco, and what I should show you are the peoples' faces while this cat was playing a piano in the middle of the Pet Store. It is like they couldn't believe it. People came up to me. I remember one lady came up to me and she said "where are the strings"? She thought it was a puppet of some kind. We would go to the bank, we would go to get a video (when there were video stores) we would go to the video stores, we would go to the dry cleaner, and Ricky would walk up on the counter they have. Other customers would come in and Ricky would give them the dry cleaning. I mean, just an amazingly social cat, amazing, and people were just so enamored and because Ricky was a Devon Rex, looked kind of unusual. Very, very quickly we went to the bank once with Ricky on my shoulder. I made the deposit or withdrawal, whatever it was. On my way out a security guard, it is true, stopped me, and I thought really I am busted, you know I didn't think. Okay, you cannot bring a cat into a bank, I'm in trouble, and he said "where did you get that?" I am thinking, like, does he want to know the name of the breeder? What does he want? He said "what store?" He thought it was from a Steven Spielberg movie. Then Ricky went "meow" right on cue.

Ricky was absolutely incredible, incredible, incredible. The bond we had I wish I could put into words. I don't believe there are words for that. So we were at the veterinary clinic and Ricky was playing the piano, everyone applauded. We began the exam and there were still lot of people in the room, in those little veterinary rooms. No matter where you are, right, those rooms seem to be small anywhere in the world, and there were like 10 people crammed in there, but the veterinarian listened to Ricky's heart. She kind of had a look on her face and the room cleared out. It is amazing. It was 2002 and I am still as moved today as I was then in some ways. I was determined, and this is why and how I joined the Winn Foundation's Board of Directors. I was determined that we needed to do something about hypertrophic cardiomyopathy. There are no hard numbers on this, but it is very possible for indoor cats between the age of about 2 or 3, or 4 and the

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common heart disease in cats, and it is really common and I was determined to do something about it.

We have raised over \$100,000 in feline medicine, which I think is nice, and I thank all of you who have given to the Ricky fund, and I hope continue to do so. \$100,000; we have done something with that money, and we are going to hear a little more about this. For two breeds of cats, the Maine Coon and the Ragdoll, as I suspect you know, the gene defect has been identified. So by a simple cheek swab we can determine if those cats have it. Breeders like you can respond. It is great, it is a great start. We need to do much more than that and to do that, we need your help, and maybe this symposium is a start of reinvigorating what we need to do. I don't want to forget about the cats with heart disease, as I will never forget about Ricky. Thank you.

Dr. Susan Little: Thank you very much Steve. So I have the great pleasure of introducing our first speaker this evening and that is Dr. Leslie Lyons. It is a pleasure for me, because I have known Leslie both professionally and as a friend for a great many years. So, I could tell you about the stuff that is on the slide there; about her undergrad and her graduate work at the University of Pittsburgh, and I could tell you about her time at the National Cancer Institute working on the Feline genome project. As most of you know, in 1999 she moved to UC Davis and setup her feline genetics research lab and has been responsible for many of the important advancements in feline genetic research that we have seen and continues to be so. Winn has supported Leslie for many years as you know. I'm sure most people in this room are familiar with the work that Leslie has done and it has touched you in some way. But there is another side to Dr. Lyons that I wanted to tell about tonight and that is because I have a very special and important role as a board member of the Winn Feline Foundation. I am the only board member to have this role. No one has had before and probably no one will have it after. My job is to follow Dr. Lyons around the world and ensure the safety of our investment in this investigator, because she likes to do things like bungee jump. I am the one who gets to take the pictures and the video because, notice, I am the intelligent one, I am not jumping. So that video was taken in South Africa last summer and the picture I think is near Victoria Falls in Zambia. So I am happy that I brought her back alive from that event, but it is that courage, that, you know, resourcefulness, that love of a challenge that takes Leslie around the world to do things like that, that has made her an outstanding feline researcher. That has enabled her, I think, to push the boundaries forward and really to change the game for us in feline genetic research. So with pleasure, I bring you Dr. Lyons.

Dr. Leslie Lyons: Okay. Are we good to go? Excellent!

Thank you very much Susan for the introduction. One day, I can get even. I have my own videos and things too, but at least every time I am out doing some of those things, we are collecting cat swabs wherever we are, so there are few things. I will try and speak lightly because I think this is turned up a little too high. So I am going to kind of walk us through where we have been for the past, I guess you know I realized it has been 20 years now that I have officially been involved with cat research. When I moved to the national cancer institute in February of 1992, that was beginning of my cat world, and so it has been 20 years and I am quite pleased that we have actually solved one of my 20 year projects, which we will talk about. So I am going to try to show you how things have evolved, and what we can do now with DNA projects, and we will be moving quite quickly forward. But over all these years, the Winn Foundation has been right behind me.

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Certainly, our biggest funding comes from the National Institute of Health. So I always do, although I know everybody wants me to work on silver, I always have to put disease projects at the top, because that is what the NIH wants you to do, but give me a moment, and I can turn any cat trait into a genetic problem that NIH would be interested in. As you know, I am at the Center for Companion Animal Health and Niels Pedersen is right there with us. He is actually the head of my cat colony, but these are the guys behind me that actually do all the work. So I want you to keep in mind when you are funding our lab, you are funding students to become geneticists, become interested in cat genetics, and hopefully their lives and their careers. So Barbara is who found a couple of these things that I will discuss today. Barbara 'the Italian' is what we call her, and she will be joining us tomorrow night and be speaking at the Burmese thing as well on Saturday when we talk about the craniofacial defect.

So, as we already know, cats are a wonderful pet and they are certainly taking over as far as being one of the most popular pets in the United States. One third of the households in the USA have cats, but of course most of them are not our fancy breed cats, which are the ones I tend to work on. But over the past 10 years, cats have really jumped forward in research activities. So as you know, there has been cloning of the domestic cat and everybody thought that was a big hit for a while. They were going to sell cats and then they realized, well that is not really a lucrative process, so they don't do that anymore, but we have also made glow in the dark cats. So there are green and red fluorescent protein cats, because we are trying to work on transgenics. Now that I have found, or many people have found these genetic diseases, we can prevent them from happening by a genetic test, but what can we do about the animal that actually has the disease? Maybe we can do gene therapies, and that is why you develop a glow-in-the-dark animal, because you are trying to show that you can do a gene therapy, right? It is not just to make a glow-in-the-dark cat, but we are now learning that we have the technologies to be able to do things like that. But, so far, in the past, what generally has happened with genetic projects are things called candidate gene approaches. We have basically stolen the information from other species and used that and helped to try to translate that in the cat. So that is how we have found a lot of our genetic traits over the past, say 20 years or so, but now life is changing and I am going to show you how we work away from this.

So this is called comparative genetics, comparative medicine. It is the candidate gene approach where you actually use a gene from another species, analyze that gene in the cat, and see if you can come up with the proper mutation. So that was used in the early 80s or so to figure out the gene that causes gangliosidosis in korats, and that is one of the first genetic tests that has been available, and because you had a biomarker that was out of whack, you could kind of guess what gene would be involved. These conditions occur in other species. They have already been worked out, well gee, let's look at the same gene in the cat and see what happens, and sure enough you find the mutation for different types of gangliosidosis. It took a lot of work back in the 80s to do that because you didn't have a lot of genetic sequence for cats but that is how we approach things. Through the same technique, when we found out the mutation that breaks this enzyme that converts these two different types of acids; so this acid here is what is on your cells when you are a type B cat and this is a type A cat. When this enzyme is broken, you are a type B. All we had to do was read the literature, and within a month, we sat down and said "Hey, it is probably this gene, lets analyze the gene in

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the cat" and sure enough we found the mutation. So a student came from Italy. She wanted to work on dogs. I said "Go ahead and read the dogs, but you've got to read about cats too." She read about the cats, came in and said, "You know, it has to be this enzyme in the cats, the dogs I cannot figure out yet." I said "Well do this while you are working on the dog stuff", and within a month she had the mutation for type B blood type. So it wasn't quite magical, but you are being smart enough to pay attention to what work has happened before you. This is also how a lot of our coat colors have been figured out. This is the pathway to produce colors, eumelanin is black, pheomelanin is yellow. Those are the only two colors that are in your cats. Everything else is an optical illusion. So it all starts with tyrosinase and the different enzymes along the way are the things that sometimes get broken or altered, that lead to our coat colors. So one of the things in the pathway is actually Agouti so we have found the mutations that make one mutation takes out the yellow pigment in ticked fur here, and that makes a black cat. So there is only, in what looks to be a brown cat, that is black and yellow fur, that gives you the optical illusion that it is brown, and you have a black cat.

We have also found the mutations for Siamese and for Tonkinese, Burmese, for the different brown color variants. That was all done by candidate gene approach. We knew what these genes were in mice particularly, that is really where the research was done. We looked at the same genes in cats and were able to find these mutations. Now also we sit and we wait to see what happens in other species. So other researchers have done work on a keratin gene called keratin 71. They published a paper on dogs and found the curly coat, the Portuguese water dogs, and the wire hair of a couple of other dogs, and they said "Well hey, we have curly coated cats and wired haired cats, let's take a look at those same genes." Sure enough keratin 71 is not only the mutation for the devon rex's curly coat, but, you know, people like Robinson and you guys had already kind of figured out "Well, we think hairlessness of the sphynx is in the same category as well." So what use to be considered two different loci, devon curly and sphynx hairless, that is actually mutations at one gene, that keratin 71, that caused, that pretty much just knocked out that gene, and the sphynx is dominant to the devon rex. The devon rex has to have two copies for it to be a curly coated cat. sphynx then, of course, can carry devon. We have also, through a candidate gene approach, found the mutation for little white feet, gloving. And this was fun because, did the ragdoll steal the birman white feet? And the answer is no. They did not. There are some ragdolls in the world that look like they do have some birman cross in them, but overall the majority, whatever is causing the mutation for ragdolls to have mitted feet, it is not the gloving of the birman cat. So you can actually genetically test and prove whether your mitted ragdoll has come from breeding with a birman or not.

Then kind of finally, we have always wondered about the new mutation that has been found that is called amber, and that is found in some Norwegian forest cats. This is in a gene called extension MC1R, and the point is, everybody has always wondered, that has always been the first gene that everybody has looked at. So orange, everybody look at MC1R first and then that was wrong. So everyone has always wondered where is this mutation in cats? Because in horses, that is what causes red horses. Can anybody name this horse here? This is Secretariat. This is the one that was just going to win and then didn't run in the Triple Crown, so he is a red horse as well. So red takes the black hair of the mane and makes it into red. Red pigs are also extension mutations. So we have known these for a long time as well as yellow labs and stuff. Red

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hair. So we have always wondered, "where is extension"? So when the amber cats came along, at least the researchers were like "there it is! Very cool. Alright, finally we have one" and stuff. But this has been known for a long time and was one of the first coat color traits ever known in humans, dogs, and horses. So finally we have the same gene in cats.

So a lot of our genes have already been found by what we call the candidate gene approach. We basically took a shortcut and used what we had learned from other species. Then we kind of evolved into what are called family-based studies. So that is where I was always bugging you to say "Hey, I need your cat that has FIP, but I need the parents, I need the grandparents, I need the siblings, I need all that," so that I can build up pedigrees of cats and families of cats that have interesting traits and problems. So the point is, you have to have very large extended families to do these types of studies and this has been my life for the past 18 years; it has been truly trying to build family-based studies. Genotyping, so actual genetic testing in all these families is very laborious and takes a lot of time. You tend to need to have traits that are clearly dominant or recessive, and the statistical analysis is called a linkage analysis. So we would have to have 2 to 500 polymorphic markers. Those type of markers, if you have ever heard me talk about microsatellites or STRs, those were the type of markers that we wanted, and they are little repeat units that are just found all over the genome. They are very highly polymorphic, meaning they are very informative in many different animals, in different individuals of a species. So you guys know about these because if you have ever watched CSI, this is exactly what they are doing. So when they take a little buccal swab, they are going to run a gel that looks like this. These are different genetic markers, different STRs that ends up looking like this. Sometimes you will see a printout, they will put a printout on a screen that looks like these bunches of peaks and stuff, so that is basically this gel turned sideways, and a laser is used to read the intensity of the peaks. Then, from the sizes up here, we actually figure out the sizes of the different alleles of the individual and that is how we just genetically type individuals for STRs. So this is a DNA profile. We can do these DNA profiles with cats, for humans, for pigs, for dogs, but they all use different genetic markers. We needed it in family-based studies, some 500 of these that we would have to type in all these different individuals of a family.

Here is an example of it done in a small family, this is a small family. The black circles and squares are individuals that have polycystic kidney disease. Here we have the genetic markers and their genotypes down below, and we figured out that for polycystic kidney disease, this allowed us to figure out what chromosome it was on and then what kind of gene to look at. So by figuring out what chromosome it was on, we could guess, if it was on a cat chromosome, what we call A3, we knew to look at all the information that was on human chromosome 2 because we knew how the cat chromosome matched to the human chromosome. By doing that comparative approach, we knew that on human chromosome 2, there was a gene that caused human polycystic kidney disease. So, hey! That is the gene we are going to look at. Now why wouldn't you just do that right at the very beginning? Well, because if we look at polycystic kidney disease in the cats (never expose who your clients or patients are, right); it is a dominant trait. We could only be very certain that we knew how a cat would be affected by doing ultrasound at about eight months. That was after you wanted to make decisions on your cats and stuff. There are also liver cysts but kidney cysts are the primary presentation, but there is more than one type of this in humans. So there is more than one gene known in humans that causes polycystic kidney disease. So by doing this comparative approach and having good

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ultrasound, so this is ultrasound with what the cysts should look like in a kidney with PKD. This is kind of what a cat can look like. So most of our cats are very mild, but some cats get very severe disease and by the age of 2 to 3, they can have a kidney like this. What is amazing is before this cat was dead, it was alive and it had a kidney that looked like this. So it was limping along for quite a while. So cats are quite amazing, that they can be pretty bad off and then suddenly go downhill, but this is very similar to the human presentation as well. The point is, one DNA mutation, one DNA nucleotide was out of whack in this huge gene, and here is just to show you; the gene has 46 exons. It is 3 pages long. We did not want to go looking for that gene unless we knew we had the right gene because that would have taken a lot of time and money, and out of 46 exons, a very large gene, one base pair is out of whack, and that is what causes polycystic kidney disease. So quite a remarkable disease. Exact same condition in humans and in fact in humans, you have heard about cystic fibrosis, you have heard about sickle cell, you have heard about Duchenne muscular dystrophy. PKD is more prevalent than all three of those combined. You never hear about it because it affects old people, and nobody cares about us old people. So by the time you are my age that is probably when you would start going into renal failure with polycystic kidney disease. Let's save all the young little kids that have CF and stuff like that, but this is the second reason, biggest reason of why people are on kidney dialysis behind being diabetic. Usually, if you are on kidney dialysis, you last about seven years, and usually someone with polycystic kidney disease, by the time they are 60, they are on renal dialysis. So that means they generally have a 10 year shorter life span than other individuals.

So we used to do genetic tests that kind of looked like this. This is the normal allele for polycystic kidney disease. This is an affected cat, and we can see that the affected cat always has the normal allele as well. We never find cats that have two copies of the mutation for polycystic kidney disease. That means they are dying in utero. They probably get formed as an embryo, but then die very soon. Kind of like the manx trait in the tailless cats. But, from there in early 2000 to 2006, the NIH said "Okay, these cats, we are kind of noticing that they are kind of important, let's do some DNA sequencing effort." So they did what is called a light-coverage DNA sequencing effort, and we got stuck in there with the armadillo. Why would you do an armadillo? They are a great model for leprosy actually. So armadillos, guinea pigs, elephants, tree shrews and the bunny rabbit and a few bats got sequenced at the same time as the cat. But it was a very, what we call light coverage. They didn't really do a real strong job like they did for mice and humans. But, by being able to do that and do still linkage-based studies, Dr. O'Brien's group, Marilyn Menotti-Raymond working with *Kristina Narfström*, they were able to use that same approach to find the mutation that causes retinal degeneration in abyssinians, so a recessive mutation in the gene that is called CEP290. Now, what has been interesting is once you go out and actually you genetically type cats for CEP290, you see that abyssinian observed heterozygotes, so those are the cats that carry the mutation, certainly carry this mutation, but we can also see, look at this, some Orientals and Siamese and Singapuras are carrying that mutation as well. That was a surprise. So once you have these genetic tests, you can go out and survey your populations, and see who is at risk as well. So there are a few blind cats out there probably, that we either don't recognize, don't know about, but the disease can have a very slow progression as well. So by doing these genetic studies we can actually find other breeds and population that are at risk.

So, so far here are some of the diseases that we need to worry about in our fancy breed cats. We have one major form of PRA. There is a second form, but it is not as important to the fancy breed cats. Pyruvate

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kinase deficiency is certainly very important in abyssinians, but we have also seen it in ocicat, Bengals, some Siamese and very significant in singapuras as well. We have different types of gangliosidosis in Burmese. In the UK, hypokalemia, it is a potassium disorder that affects Burmese. We have just been able to find that mutation this year and I will tell you about those studies as well as now we also know the mutation that causes the craniofacial defect in Burmese cats as well.

So we have quite a few different genetic mutations that we have been successful to date using these old style approaches. Linkage, family-based linkage studies and candidate gene approaches. We have found a lot of the different colors and there are certainly more on the way. People are looking at inhibitor. I know the mutation for orange has been found, so that will get introduced soon this year, and also probably a mutation for one of the tabby genes as well. So one by one we are starting to knock these off. Primarily, I have been interested also in studying our fancy breeds and understanding their domestication, but I have an ulterior motive to doing that. So I will tell about the ulterior motive, but I will tell you first about the fun thing that was important for you guys.

So we did microsatellites, so those old-school markers on over 1000 different cats from up to, now we have about 29 to 30 breeds that we have done, and we have actually now done different types of markers. We went to Egypt and collected cats in Egypt. We were actually looking for, we were trying to figure out the site for cat domestication. Wild cats use to live in all these areas that are colored, but we think there were three different sites where human beings settled down and independently developed agriculture. One was in the near east in the Fertile Crescent. That starts around Baghdad, goes up into Turkey where the Tigris and Euphrates rivers are, and then down the Levant, which is where Israel is, and into Egypt. Then there is an area called the Indus Valley, which is right on the border of Pakistan and Indian, and then also the Yellow River region in China, so very distinct regions 10,000 years ago. There was not a lot of transport at that time. So we are trying to figure out if cats were domesticated more than one time. We certainly know cats were at least domesticated in the Fertile Crescent from the African wild cat, but we are still trying figure out about the South Asian cats which are very special too. So there might be second domestication site, but we have to figure out a way to prove that.

Along the way, by doing these studies, we have been able to figure out that there are 8 major races of cats in the world. So we tend to say that there are races of humans, right? So now we kind of think that there are 8 major races of cats; European, Mediterranean, Egyptian, Iraq/Iran, cats from the Arabian Sea area, cats from the Indian ocean area, South Asia, and East Asia. So if you send me a DNA swab from your cat, we can actually tell you whether it is one of these eight major races of the world, and that includes your Monty cat, your just household pet, your random bred cat. We can match it to one of these races. Most cats in North America are going to be European cats. They came with Columbus, right? They came with Magellan and Cortez and so they are European cats that came over with those great explorers and stuff, and also are migrants as migration came to the United States. But, there are still other very interesting and diverse populations of cats. We did find out that cats from Southeast Asia, for example, so this group here, the South Asian cats, have led to the development of specific breeds. So the Siamese, the Singapura, the Burmese; these cats really do come from South Asia and their nearest relatives are the street cats of South Asia. Most cats come from Western Europe, most of our breeds. Some of the breeds come from the

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Mediterranean such as the Turkish van and Turkish angora, and then one breed, the sokoke, looks like it is that Arabian Sea breed. I know it is not a very popular breed, but it is something that has been just developed in Europe and stuff. So one, two, three, four, four of the different races have led to the development of our cat breeds. So this will become important as we hopefully develop crossing programs for our cats. I do need to mention that we have looked at bunch of different breeds, but the breeds don't all fall into genetically distinct categories. So if we count two breeds as Persians and exotics, if I look at them from a genetic point of view and I am not biasing myself by saying this is a Persian, this is an exotic. If I just look at them from their genetics, I cannot separate them as two different gene pools. That is because one genetic mutation does not make a breed. So, short haired Persians, there are long haired exotics, they are Persians. So that is I know a little controversial, but so we can see that, for example we can see that the Havana brown is kind of mainly the same color as the Siamese. So they are just a solid chocolate point. They are basically the same thing. So we can see which breeds are genetically distinct and which ones are not. More recent studies have shown that Scottish folds, even though you had the fold mutation, they are becoming very much like British shorthairs and British shorthairs are actually becoming very much like Persian. So that is kind of very surprising as well. So a little too much crossing going on between British shorthairs and Persians. You can't fool the geneticist, so I know what you have been doing.

So our inbred cats..... You know I would like to understand, why do people keep sending me pictures of cats with bread on their head? It's like they are in the bread, they are inbred. Oh, they are inbred cats, okay. So it took me a while. Okay, I might be able to figure out your crosses, but I am not clever all the time. So we still are very much interested in inbred cats, but we want to try to make them as genetically diverse as we can while keeping the wonderful qualities. And those wonderful qualities are temperament, color, body shape, the behaviors that they have, that they are good mommas; those are all very good and important things. But by doing these genetic studies we have been able to see that some of the newer breeds, such as Siberian, the ragdoll, Turkish angoras and manx have very high genetic variation. That is good. That is what we want because at this end of the scale that is where you find random bred cats. That is where you want to be. So as we move to this end of the scale, that is where you kind of don't want to be; you don't want to move this direction. I don't want to take this slide literally one by one saying "okay, Siamese are far better than ocicats." That is too close to call, alright? So what I want you to take home is try not to be at this end of the scale, alright? So, who do we see down there? The Burmese and Singapura. So the darker bar is genetic variation and we can see that genetic variation is on the lower end of the scale, but also importantly is this lighter bar. That is inbreeding. That is your inbreeding coefficient. You want this bar to be high and you want that bar to be low, alright? So when you have a combination of both being the wrong way that is telling you that you are having a genetic gene pool problem with your cats. So one of my favorites is korats, they are a wonderful example. How can they have high genetic variation, low inbreeding, and they only come in blue, and there are like five of them registered every year? How can that happen? It happens because they share, they talk with one another and they use genetic testing in a wise way. Not by getting rid of carriers, but by managing them over a slow period of time. I think now they have gotten rid of most of those cats, but it took them a while to get there. Also, they go to Thailand and bring in cats. They are not bringing 6 or 10 cats all the time. They are just bringing in a couple every once and a while, and the cats get shared and moved around. Not everybody works well together, but overall the majority of the breeders do,

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and so they are your hallmark. They are your benchmark. It is to figure out how to focus your cats in this regard. High genetic variation, low inbreeding and it can be done. So the korats are an example that this can be done. We need to move Burmese in that direction. I personally think Burmese are loping towards extinction if they don't get their act together and start really trying to diversify their cats. Singapuras probably need some help as well.

Other things we have done with this work, is we did a pretty diverse Turkish van study where we first did a study just with these cats over here on the left side. Those were Turkish vans that were registered in different cat Fanciers'. So those are Turkish vans, and then people sent in other samples and said "Hey, to me this looks like a Turkish van, is it a Turkish van?" And we could say sometimes since they matched the same colors they were right, but other times they were wrong. So genetically, even though they looked like a Turkish van, it wasn't actually a Turkish van from a genetic point of view. However, if it looks like a van, maybe you should add that in to help the genetic diversity of your gene pool. So we can actually use genetics to see how diverse they are, and then decide to add them in, or decide to keep them out. That is not my decision that is yours, but you can use it in both directions. Either it is a good thing, or maybe you don't want it.

So a lot of this work, we had a very nice day at Davis where we had maybe 100 cats downstairs in our clinic, and we had it all set up like a cat show, and people brought their cat, and this Burmese just sat there and stared into the camera for a good five minutes; so it runs the whole credits for the National Geographic special, and so this is called The Science of Cats, and every once in a while it shows up on Explorer on the Nat Geo channel. This has led to the development of this cat ancestry test. So if you have heard about the Wisdom Panel for dogs, we basically have the same thing for cats as well. It can be found only at UC Davis at the veterinary genetic lab. That is where you have been sending your stuff for PKD testing and coat color testing and stuff like that as well. Along the way we have been able, since we got to go to Egypt, we were able to get cats from the streets of Egypt, and we have been the first to sequence Egyptian cat mummies. That paper, it just got published. We sequenced 3 mummies, bones from 3 mummies, and we have been able to show that the cats, the genetic types of these mummies, are just like the genetic types of the cats that are running around the streets of Egypt today. So that means the cats of Egypt today are the descendants of the cats of the Pharaohs. So we did that by what is called mitochondrial DNA. Mitochondrial DNA is much more prevalent. We sequenced a region called the control region, and by doing that we are able to show that the mummies, here are the mummies, are of genetic types that are only found very prevalently in Egypt and the Mediterranean. Like type A is far more found in the United States, for example. So we did that just by DNA sequencing, and if you just look at the different base pairs here, you can see that you should have two black ones and a green. Two black ones and a green, there is an insertion of these four base pairs that kind of help distinguish those cats as being Egyptian mummified cats.

But there are still some things we don't know. Of all things, one of the first things ever genetically mapped in any species, was orange because people figured out it was associated with gender. It must be on the X chromosome. So back in the days, in the early 1900s when people were just trying to figure out how genetics worked, we knew orange was on the X chromosome. It has taken us up until now, up until this year to actually find that mutation and that has been done by Dr. O'Brien's lab. So we are just now starting to

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figure out what the orange gene is. We still have things to look at such as, we can tell you a cat is going to have polycystic kidney disease, but how many people out there, if you have a cat that is positive, continue to take their cat to the vet. Because you won't know whether your cat is going to have mild disease, this is very mild disease. The cat will probably never die of renal failure versus how do you know if your cat has this? That cat is going to die in few years. So if you have a positive cat for PKD, it should be going to the vet to see how it is progressing with its disease. We don't understand the genetics that causes this to happen. There are still things to look at.

Of course silver. I know we are going to find silver one day. So hopefully we will find that.

So now we have moved into a whole new era. So the whole new era has occurred in maybe the past two years. We have been trying to move this along. That is now, instead of microsatellites, instead of SDRs, you are going to always hear me talking about SNPs. SNPs, SNPs, SNPs, alright? SNPs stands for single nucleotide polymorphism. It is just a single DNA variant, like that DNA variant I showed you in polycystic kidney disease? That is a SNP. So the thing is, because we have been able to sequence the genome, we have been able to find these SNPs all over the place; so just one single based pair change is a SNP. We had first the coverage of the 2X coverage, the light coverage that was done by the NIH for sequencing the cat, then Hills Pet Food came along and secretly kind of did their own project, but still a very small project, but they did give all their data to the public database. So that was very nice of them. But they also sequenced different cats. So the key one you wanted to sequence was an abyssinian called Cinnamon. So everybody has sequenced that cat. But they also started doing different breeds. When you do the different breeds that is when you find the SNPs. That is when you find the polymorphism, the variation. If you only sequence one cat, you wouldn't find variation, you would only find what is in that one cat, so you have to look across different breeds. So not only did they do this, but they gave a million dollars to the Morris Animal Foundation and that becomes a key thing that happens, right? But also along the way, the NIH asked Washington University to continue sequencing Cinnamon, to do a better sequence of Cinnamon. So that has been happening as well. Our lab, you know big labs do this, this guy doesn't even know what a cat is, right? So he has to put a committee together that included us and many other researchers in cat genetics to tell them what other breeds we should sequence. So all that data that we had fun with trying to figure out which breeds are similar, and which ones are different, that now becomes the key data for the cat sequencing project, because if we only have six or seven or eight breeds that we can sequence, which ones are the most diverse that we should sequence? And now we have the answer to be able to help with that. So these are the cat breeds that we chose to sequence to find the SNPs. You have got to have them to find a lot of SNPs. So in the end we found some 17 million SNPs by sequencing these different cat breeds, and so many of you guys actually submitted, this is where I asked for blood samples, so that you could actually participate in the cat sequencing project. So the cat genome is there now. It is available to me as a researcher, so it is actually out there and it is publicly available. A huge group of people did this. When you say "Oh, Lyons is in charge of the feline genome project" that is not even close. It is a consortium. It's a big group of people. I did a small part, other people did a small part, and it all added up to a big study. But, so now this is what we have this little piece of metal that is called a DNA array. A chip. And on this chip, is 63,000 SNPs, so now instead of doing 200 or 300 genetic markers that were very hard to type in the lab, now I can do 63,000, with 12 cats at a time. All I have to do is prepare a good DNA sample. And you know what? If you take a

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good buccal swab, that's good enough DNA to run on one of these chips, but it has to be a good buccal swab. You have to send in a good buccal swab, and we can isolate the DNA, send this off, and in three weeks the company in Nebraska will send us back the data and it will be 63,000 genetic markers on how many cats we send. We can send them 12 cats at a time, or we can send him 100 cats at a time. Within three weeks, we'll get all that data back. So it is an enormous leap with the technology that has happened in the past two years.

But, now that means we have completely changed how we do our studies. So I have always asked you "Oh I have this affected cat, I need its parents, I need its siblings, I need this, I need to extend those pedigrees," right? Not anymore. Now we are focus on what is called case control studies. So a case is a cat with a trait of interest. It can be a Bobtail or it can be a cat with hypokalemia. Whatever your interest in it is, your case has the condition. The control does not. The thing is, these have to be perfect, these diagnoses have to be perfect. So we have to work very, very closely with veterinarians to make sure that we have these cats in the right category. If you're sloppy, and you have some cats that are affected and they are in your controls and vice versa, the study is going to be terrible, and you can spend a lot of money really quickly sending off that DNA to Nebraska, and then get crap back, right? So crap in is still crap out, right? So this is now what we are focusing on. So we still ask you for a pedigree because that is what we want to figure out; how related are our cases. How related are our controls? The best scenario now is to find cats that are unrelated. So now with cases if we can still find them within a breed, but unrelated, we can use them. If they are little bit related, that's still good. We can still use that, but now that's what we do with the pedigrees, is try to figure out what that kinship might be. But we don't need to build pedigrees of related cats anymore. Just case control, very fast genotyping, and this is called a genome-wide association study; a GWA or a GWAS, genome-wide association study. One of the other things that we have to look at is when you do one of these studies, how do you know how many cats you need? How many cases do you need? We can predict that from the breed analysis that I did, but the more inbred the breed, the lower its genetic variation, actually the fewer cases I am going to need for one of these case-control studies. So in this regard, this is why Burmese worked out so well, a very inbred population. This red line is American Burmese cats and of all the breeds we looked at, they are very, very highly inbred. This is called linkage disequilibrium. Their linkage disequilibrium is high. So, that is bad for the cats. That is good for me. That helps me find a trait very quickly with only a low number of cats. So remember, our pedigree studies, when we did polycystic kidney disease, there were 600 cats in those pedigrees. When we do these studies now, he can do them with 30 or less cases for some genetic traits. So with the Burmese projects, we have been able to do them with less than 30 cats. We also, from that genetic data, we have also been able to find that Western breeds, so these are all different breeds of cats, are genetically distinct from the Eastern breeds. But, if we need to do a genetic study say on something like Cornish rex, if we wanted to try to find the curly coat for Cornish rex, your cases are Cornish rex. They are curly coated. Who is your control? There are no Cornish rex that are not curly coated. So you can cheat by figuring out what is the most genetically similar population. So all that fun we did by doing all the populations of the different breeds, we now use that information for this as well. So I think I was just having fun trying to figure out how your breeds are related, really I wanted this information for all these different studies as well.

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So now we make data that looks like this. This is called a Manhattan plot because it looks like it has skyscrapers in it. So we all walk around talking about SNPs and Manhattan plots now, and what you are looking for is the highest SNP. The highest SNP is the SNP most associated with your disease. And so we did Cornish rex. All we needed was 11 cases. That was just astounding. We had 11 Cornish rex and a whole bunch of controls. The control was just a group of cats that were most genetically related, but of course did not have a curly coat. Once we looked around this SNP here, we looked to see what chromosome it was on, chromosome 1, and wow what genes are under there. Look at that. If we read the literature, there is a gene in there that causes curly coat, woolly hair syndrome in Pakistanis. And so you look at the Pakistani data, and sure enough, woolly hair in humans is Cornish rex. So give me time, I can turn any genetic trait into a human health condition. So actually the Pakistanis also have other problems, so it depends on what mutation you have in the gene. So they also have other problems other than just curly hair and stuff. So this is actually a mutation. It's a 4 base pair deletion, so we can see the curly coated cats actually don't have that.

Now also by doing this study we were able to collect, because some veterinarians in the world actually are collecting DNA samples, we were able to call up the UK, Germany, and Australia and get all their cats that hypokalemia, put them together in a pile, run 30 cases against 25 controls, and we found the mutation that causes hypokalemia in Burmese cats. This is primarily non-USA cats. So it's European cats, UK cats and Australia cats. It causes low potassium which causes seizures and muscle weakness. Their peak looks something like this. We have now called this the peak of Dubai. You know how Dubai has all the really high buildings. So we want Dubai peaks in our plots. We are also calling this a Victoria Secret plot because the Italian picks the colors of what you're going to make your chromosome, so it is Victoria Secret Dubai plot. So now you can do things very rapidly. If you have the DNA, you win. And so it still means, if you can provide the DNA from your cats, we can do the studies very rapidly. This hypokalemia study was done in three months from a point of starting the preparation of the samples, sending them off to the company, the company gives you back data in three weeks, you see a peak of Dubai; this analysis takes about a week. Then you say "Okay, there's a gene under there, let's start looking at those genes", and if you do it well, within three months you will have the mutation. So we're just about to submit the paper for this project. You still use the alleles a little bit to prove that things are inherited and stuff. So we still kind of like to collect little families, and it was just showing us that every cat that had hypokalemia had the mutations that we were worried about. In the same way, we have been able to find the craniofacial defect in the Burmese cats. So we knew what chromosome this was on. The laboratory actually convinced me to try running it on the chips. And I'm like, the chips are just going to put us in the same place. Well what the chips told us, is that the region that we were looking at wasn't small, it was actually gigantic. So when we were looking in the small region for genes that we knew caused craniofacial issues in humans, we then later found out, no, the gene is actually a very large region and there is a gene over here that is a perfect candidate. So once we looked at that gene way over here, the Italian did it. She comes into my office and it's March 29 at 9:56 AM. I'm yelling at Niels Pedersen about money. We are fighting over money. Barbara comes in and she's all shaken and she is like "We got it, we got it!" And I'm like "What are you talking about?" She's like "The craniofacial defect, we have it!" And I said "You weren't even working on that." And she said "Well I did it in secret. I didn't tell you." So it's little genes they know my accounts and they will secretly go buy primers for these genes and test them, only if they are little genes. If it's a big gene, they would not be able to get

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away with it, I'd figure it out, right? It's interesting, because in February I said "You know I'm getting all these invitations to talk here, and in Australia, and in Portugal. I can't face these breeders anymore. We have to find this." We had the data. Barbara is one that she sat down and actually looked at it, and she is one that found the mutation. So she will be here on Saturday to talk with the Burmese breeders and stuff.

This is a very interesting mutation because one copy causes short face. So one copy of the mutation causes brachycephaly. They have been wanting to find the gene in dogs for brachycephaly for several years. Ha! We beat them to it, right? So dogs, they have genes that kind of suggest brachycephaly, but we have one. Now, it's not the best gene in the world to have, but at least we now have the gene that causes nasal facial structure. This is actually what it causes when you have two copies of it, so a very severe malformation. This does occur in humans too. You can actually look this up, see with the gene is, put hair on the human, and it'll look just like the one of these Burmese kittens.

So, again, there are still probably other genes that cause short face. This is not the gene that causes brachycephaly in a Persian cat. So we still kind of want to look for genes that are involved with facial structure. We still want to find genes that affect why cats have liver cysts with polycystic kidney disease. We want to figure out why some cats get fat and others don't. We can start to do these studies by using these DNA arrays. We are interested in looking at deafness in cats. So we have an active funded project funded by the Winn Feline Foundation. The thing is, you think your cat can hear, but are you sure they can hear in both ears? That is the question. So anybody that has a dominant white cat any breed, a deaf cat, you can pretty well figure out if they are deaf, we want them, but we need to find the controls, the cats that can hear, and we have to kind of do BAER testing to make sure they can hear in both ears. So the khao manees, the Persians, the Turkish angoras, anything that comes in all white, we are interested in. We don't understand the genes that cause variation in blue. So these are things we can do. We are still actually looking for some retinal degeneration genes as well. So with that, we will probably end there.

So we were looking for all different types of genes and mutations that are affecting our different breeds. We have new projects on amyloidosis, on lymphosarcoma. Rag dolls have this condition where they are missing one kidney and maybe also an ovary. Egyptian maus with stones. So there are lots of things that we can do if you can get the DNA samples in. Once we get up to 30 or 40 cases, we are a go. So we have a lot of strong tools to go after different genetic traits at this point. So we still need your help. We still need the help of the veterinarians that get the diagnosis right, but we have very powerful tools. We have a new era for genetics in cats, and we can make a lot of good progress by obtaining your help. Thank you.

Steve Dale: How are you all doing? Good! Thank you very, very much Leslie Lyons again.

Is Joan Miller is sitting in the back of the room somewhere? Joan are you here? I heard she was here. One of my colleagues Wendy Christensen is here who is a wonderful cat book author. Wendy raise your hand.

Joan is where, (next door), okay, at a meeting. Well in her absence because she is usually here. We would not have the Winn feline foundation symposium if it was not for Joan Miller, a round of applause for Joan. She was once the president of the Winn Feline Foundation. This is a very special movement. We really should have secret service I think in the room because we have a president and two ex-presidents by my

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count. Susan Little who you met of course, standing right here next to me. Ex-president former past president is a better way to put it of the Winn feline foundation, Susan stand up. Betty White, past president of the Winn Feline Foundation; our own Betty White! This is Betty White. Our current president and boy she is wonderful, Vicki Thayer president of the Winn Feline Foundation. There is Joan Miller walking in to the room to applause and a standing O! I think. She deserves it. A lifetime, I do not know of anyone. You know I just wrote and this is true. The AVMA convention is coming to I think your house, right? Right down the street from her house and I said you have got to go to this so I wrote the person at the American Veterinary Medical association and I said I do not know who the top ten would be of people who have done for cats over the past several decades but whoever is in that top ten, I am not sure but I do know Joan Miller would be among the top three or four. Wouldn't you think so? She has done so much.

Speaking of people who have done a lot for cats, the Winn Feline Foundation for the past several years has created the Winn Feline Foundation media appreciation award. This is for one of my colleagues, a member of the media who has done special things for cats. It depends on what time of the year we present this award, it varies. We thought we were in Boston. Well the winner this year happens to be a Bostonian, is that the right way to put it? Is that appropriate? But she cannot be here. She had surgery just a couple days ago actually and the good news is Darlene Arden the recipient of this year's award. I will tell you the award means something but is meaning far more to me because she is a friend of mine is that she is doing very well.

Darlene has been a champion of cats for a very longtime. She is very famous in the dog world, among her books 'Small Dogs, Big Hearts', 'The Angel Memorial Hospital, Book of Wellness and Preventive Care for Dogs' and of course this book that you all have. You have got to have this in your library. It is called 'Rover, get off Her Leg.' Really that is the name of the book. Darlene's current book is called, 'The Cat's Meow' and I will tell you however many years ago it was I interviewed Darlene for something and Darlene said 'You know what cats are petty loyal and people do not consider them as such and cats are not getting the due credit that they should get.' This was about 10 years ago. I think we are all catching up with Darlene now, right. Veterinary medicine and shelters are paying attention to cats. We are at least starting to in the way that we have not done before. The name of the book is 'The Complete Cat's Meow,' everything, *everything* you need to know about caring for your cats.

Darlene is a former actress and dancer here in the Boston area and she now is a judge for K9 Freestyle, which is dancing with your dogs. I actually have... Well there is nothing funny about that. Have you ever seen that on TV? Well you know what they thought dog agility was crazy and now there is cat agility, right? So I expect to see Feline Freestyle, dancing with your cats. That would be fun. I wonder who would leave in that case. Darlene is on the phone, so I want (she is hearing all this). How about a round of applause?

A Boston native, a friend to all animals for many decades, I am honored and privilege to present Darlene (though we could have skyped it and then she would see it) with the Winn Feline Foundation media award. Sadly I have no bungee jumping video for this. Feline cardiomyopathy, hypertrophic cardiomyopathy means a heck of a lot to me (I'm disconnecting Darlene and I think I did) because of reasons that you heard before. I hope that you consider telling your friends about it. I hope you consider giving to the Ricky fund. I hope

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you consider talking your veterinarian, so when a cat passes away and sadly so many do of HCM, maybe a contribution will be made to the Ricky Fund.

(End of Session)

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