



# WINN FELINE FOUNDATION

For the Health and Well-being of All Cats

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**38<sup>th</sup> Annual Winn Symposium – June 30, 2016**

**“Cat Tales” of Genetics and Behavior**

**Transcript of Audio: Introduction and Dr. Leslie Lyons on Genetics and Precision Medicine**

## **Introduction**

### **Dr. Glenn Olah:**

Good afternoon. My name is Dr. Glenn Olah and I'm the president of Winn Feline Foundation, so thank you for being here. Before we get started with our speakers, I was going to talk briefly about Winn. I'm probably speaking to the choir a bit about Winn but, first of all, the title of this Symposium is “Cat Tales of Genetics and Behavior,” 38th annual Winn Feline Foundation Symposium, so we've been doing it for a while.

So, Winn. Our mission as a nonprofit, we were established in 1968, so we're coming up on our 50th anniversary in a couple of years, so that's pretty exciting. We support studies to improve cat health, and we also have a mission that involves education, and people always forget that component of it. We have two missions; to fund research in feline health, as well as to promote education in feline medicine and health. Anyway, we definitely are probably the leader in feline medicine regarding funding research projects and I'd say, in the last 5-8 years, we've started collaborating with a lot of other organizations that are like-minded to Winn; organizations like AAFP, American Association of Feline Practitioners, and AVMF and so on. There are a few others. So, the amazing thing to me is the far-reaching impact that Winn has had in feline medicine, and how often I find out that people aren't aware of this. I mean, these are big things. If you look at something basic, like blood groups, that was determined by Winn funded research. The discovery, in the 1980s, of feline immunodeficiency virus, FIV. One of the big ones is to find out the inadequacies of the feline diets back in the 80s, to find out that they didn't have enough taurine in their diets, that was a Winn-funded project from Dr. Pion. Measuring blood pressures, you know, it's about 30% of cats with chronic kidney disease have hypertension, so all those old cats, we should be measuring those blood pressures. Screening tests; the retroviral tests for FeLV, FIV. Showing that early alteration is safe and feasible; let's say whether it's the age of the cat, two months old, or let's say under two pounds, a cat that is actually safe with the right anesthetic protocols, we are able to spay and neuter these cats safely. Diabetes – that's a big one – diabetes mellitus. The way to really look at diabetes, you don't think about it this way. Cats are like people – they're type 2 diabetics, but they become insulin-dependent, because it's a little bit more advanced by the time the client needs to bring their cats to the veterinarian. The way I would look at it is, the diet, the weight loss, is your primary therapy. The insulin is a secondary therapy so, eventually, you hope to get them off insulin, and then you have a high-protein diet that can keep the diabetes, hopefully, in remission. We funded those studies in the early 2000s. Dr. Reinero at the University of Missouri is looking at asthma and various treatments for asthma, including stem-cell research, which I think is fascinating stuff, so tomorrow morning I'm going to be talking, just briefly, to the Association, and I will mention some of the stem-cell research that we're funding, in particular regarding stomatitis.

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I don't know if you've all seen stomatitis, those painful, painful mouths in cats that are really sad because it can be so painful that it can even lead to the point where you decide that euthanasia is humane. Polycystic kidney disease, I think that's Dr. Lyons. One of the big things that she's done is identify the gene that is associated with that particular condition, hypertrophic cardiomyopathy in Maine Coon cats. FIP diagnostics. I'll talk briefly about that as well tomorrow to the Association. A lot of advances have been happening regarding FIP, I'd say in the last, believe it or not, 3-5 years' timeframe, and we used to say, wow, what about things 10 years ago, there was a big lull, but the reason that things are sort of accelerating, at least partly, is there are two big things that came on the scene in the last 10 years, and that's SARS and MERS. Those are coronaviruses in humans, and people freaked out about that, and now they're looking at coronavirus in cats, and all of a sudden, things are really going forward. Just making a plug for Winn, I'm proud to be a part of Winn. There's a booklet that's on all the tables. Please take those. There is a lot of information in there. There are goodies. You can learn more things about Winn. I think Vicki, our Executive Director, is sitting right over here. I think she said she'd put a KitKat in there? [Laughs]

The format of this Symposium is that there are two speakers. I'll introduce Dr. Lyons in just a second but, in the center of the table, there is a pad and some pens. Write your questions down there and then, at the end of both talks, we'll have a question and answer period. I think this is more important for any of the veterinarians out there, for the RACE qualification, if you could fill out the evaluation form, that would be very much appreciated, and then, outside this room, one of our board members, Susan Gingrich, she has made these little magnets you can put on your car to promote Winn, and I think she's selling them for around \$10, and that money would go to research funding for Winn, so if you're interested in them it would be nice if you would check them out, if you didn't when you walked through the door.

It is my pleasure now to introduce our first speaker, Dr. Leslie Lyons. Let me say a few words about you. Dr. Leslie Lyons is an associate professor at the University of Missouri School of Veterinary Medicine and Surgery. She is originally from Pennsylvania and received her graduate degree from the University of Pittsburgh Graduate School of Public Health, Department of Human Genetics. Both her master's and doctorate degrees are in human genetics, specializing in both laboratory and data analysis of human disease gene mapping. In the 1990s, while a post-doctorate at the National Cancer Institute, NCI Laboratory Genomic Division, she helped organize the Feline Genome Project. Dr. Lyons developed a feline genetic mapping pedigree using natural mating and assisted reproductive techniques between domestic and Asian leopard cats. She was promoted to a research fellow at the NCI and expanded her interests by initiating population genetics into these gene mapping projects for the domestic cat. After NCI, she joined University of California at Davis and recently moved to the University of Missouri. Dr. Lyons' laboratory, The Lyons Den's, major focus is the genetics of the domestic cat, including genetic diseases, inherited diseases, and population diversity.

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Dr. Lyons' research laboratory has had success with identifying the genes causing Persian cat polycystic kidney disease, as I've already mentioned, Burmese hypokalemia, the Burmese craniofacial defect, several coat traits in the cat, and mutations causing cat blood group B. Each of these mutations can now be used as a genetic test in cats. The Lyons laboratory has been used to confirm the cloned domestic cat and African Wild cat and also the first green fluorescent protein cat. Studies have included the analysis of original cat breeds and the sites of cat domestication, which resulted in a documentary in National Geographic.

Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle. President Obama announced the Precision Medicine Initiative the State of the Union address in 2015. Most medical treatments have been designed for the average patient. Precision medicine gives clinicians tools to better understand the complex mechanism underlying the patient's health, disease, or condition, and to better predict which treatments will be most effective. Today, Dr. Lyons will discuss the role of precision medicine in the future of feline medicine.

## **Dr. Leslie Lyons:**

Welcome to Las Vegas! Viva Las Vegas. Anybody seen an Elvis yet or anything like that? The guy in the taxi asked me where I was getting married. I said "Well, I'm not opposed to that, but I don't think it's going to be this trip." I am most pleased to be back here for the Winn Feline Symposium. I've done this once before, and now it's 38 years or so. I actually did some of my homework and counted up how long I've been involved with Winn, and so our first grant, when I was at the National Cancer Institute, was I think '94 or '96 or so, and so I'm going to walk you through some of that history of us working with Winn Feline Foundation. I have to say that Winn has always been at my side, sponsoring many of our different projects, so we obtained funding from all kinds of different sources; National Geographic, we're working a lot with pet food companies, Zoetis has made some donations to Winn, and they have made donations to us as well. We also have a give-direct site for our 99 Lives Project, right at University of Missouri, trying to do like a GoFundMe type thing. So, there are lots of ways to support cat research, and the most direct ways are absolutely through the Winn Feline Foundation, so please, continue to support us and help us do good work.

Of course, I study inbred cats. It took me a while to figure out, why are people sending me cats with bread on their heads? Until I realized it was "in-bread" cats. I was just asked when I'm going to retire, and I'm like, "I'm 53, dude. I'm doing alright!" However, I think we will be moving to looking at more things in just random-bred cats as well in the near future, so I'll end the presentation with some things about that. As mentioned, precision medicine. This is the new buzzword. Every few years, in genetics, there is a new buzzword. It's nothing different, if you hear the words One Health, that's all the same as precision medicine. It's the same as comparative genetics.

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I started out as comparative geneticist, doing things in a cat that you would normally do in a human, or a mouse, or something like that, but now, everybody has to always come up with a new word. Basically, it does mean we now have the capability, instead of just doing population-based medicine – here, let's just give everybody warfarin to help reduce blood clots - now we're finding out that some people don't respond very well to warfarin, and so now we're starting to understand why some of our experiments don't work, or why treatments don't work, and it's because of our genetics, and so Obama launched an official initiative. Primarily, we hear about precision medicine when it comes to cancers, because we do know that cancers are really fine-tuned to the type of cancer you have, what kind of receptors are on that cancer, and then, once the cancer maybe escapes remission and comes back, we now actually genome-sequence that tumor to see how the genetics have changed of that tumor, and now what is the new next chemotherapy that we should give to try to battle that cancer, but it can be done with all aspects of our health, and my job is to make precision medicine work for cats.

I thought I would give you some examples, and here's myself. Has anyone ever heard of 23andMe or you've seen Ancestry.com? Well, I did it, and I did it long enough ago that I still get the answers to my health stuff now that they've put a little kibosh on that; the FDA went after them and stuff, and I would tease my mom, too, my brother and I would tease my mom and say, "We're not really your kids," so she did it as well and, unfortunately, I am the product of my mother, but I am 25% Italian. My mother is half Italian, so I am 25% Italian, so that did work out, and the rest of me is from the UK, basically, so all my father's side and my mom's father was Welsh, so that did actually work out. You can also look at this and see how much Neanderthal you are as well. So I'm 2.8%, which is about the average for everybody else, you know, but why you do things like this, it's not important that I read these diseases to you, but if you're of Catholic descent, or of any other large ethnic group, strongly, there are certain diseases that are more common in your population, so one of those is Mediterranean fever. When there are four yellow stars, that means it's a mutation, you know, it's on or off. It's a simple genetic trait. They have very high confidence with it, and look at this, I'm very clean, man! I don't have, really, any genetic traits I need to worry about, so that means I've got to start taking better care of myself. I'm ruining myself from the nurture side. I'm getting fat, drinking too much Coke and, where I have good genetics, I should be appreciating that. Beta thalassemia is something that is very common in Italian populations. I don't have that. Hemochromatosis is also common in Italians and, actually, my mom is a carrier for that. We had no idea, and then, once we did that, we found that she's a carrier. This one is alpha anti-trypsin deficiency. My dad died of COPD, but at the age of 84, and he smoked Lucky Strikes all his life, so I know, okay, at least I don't have the gene that gives you risk factors for having COPD, so hopefully I'll just stay away from cigarettes as much as I can. The more important thing is we're getting around to looking at a lot of drug sensitivities, and this is where the precision medicine comes in, that if you go in and you're epileptic, and you need to be given a treatment, they will now genetically test you to see whether that treatment is going to work on you in the first place, instead of trying it for a couple of weeks and figuring out, hey, that didn't work. One of them that I noticed here, why I first did this, is that I alcohol-flush.

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When I drink alcohol, I flush. Well, that's common in Asians, because they don't have the right alcohol dehydrogenase. I was like, "Okay, is there an Asian in my background somewhere that I don't know about?" That's where we got to agitating my mom and stuff. In the end, I don't have that mutation. What I have is I do not metabolize sulfa very well, so I found this out also, I take a sulfa antibiotic, I get a rash. So what else has sulfa? Sulfites. Alcohol. So wines that have sulfites in them, you'll see that I'll immediately flush because I can't metabolize that sulfa very well. This is where we want to head, and this is where medicine is heading all the time, whether you do it one by one, testing these genetic traits, or whether you send in your blood sample and you do a whole genome sequence, and so that's where we are now. You do a whole genome sequence, and you find out every variant in your body and stuff, and so you come up with risk factors. One genetic test that we worry about in cats is the hypertrophic cardiomyopathy. That is a risk factor. We're going to find that most of our genetic traits are actually risk factors. We've been knocking off the easy ones to date, the simple on-off traits, but we're going to find there are more and more, and now I bet you've been hearing about genetic mutations conferring risks to FIP, and so it's time to try to take a look at those in a population-wide study and see if they actually are working or not, and what those risks actually incur, and so we can see that I have a slightly higher risk for venous thrombosis, but I actually don't need a lot of warfarin to get rid of that, so that's good.

So, what about cats? The thing you have to remember, comparative medicine, comparative anatomy, comparative genetics, cats and humans all have about the same amount of DNA - 2.80 gigabases. These are the cat chromosomes. They actually look fairly similar to human chromosomes. Dogs look a lot different. We have 18 what we call autosomes, and the XY pair. This is two X's down here, so this is a female. This is called a karyotype, and all the genes, and we now know there are about 20,000 to 21,000 genes in the mammalian genome. Cats and humans share, basically, all those genes. Where they'll vary is some immune function genes, olfactory genes. Cats might have an expanded olfactory repertoire compared to humans, but we all have the same genes. The key we are now finding is actually the regulation, and this is actually making things hard, because the things that regulate genes are not in the coding part of the genome, not in the exons of each gene that make the protein. They're upstream, and they tell the protein turn on, turn off. Turn on at this time, turn off at this time, and that's really what is making us different, but those mutations are harder to find.

With cats, we could do a 23andMe. In cats, actually, I want to call it 19andMew, which fits well now that I've moved to Missouri, which is MU, right, so it all perfectly fits! Most of your coat color genes are actually found. Orange is known, but they're still doing some work to prove it. Tipped is being worked on, and we're always still trying to work on silver. Many of your prototypes are known. A couple of other ones are still being worked on by Dr. Gandolfi. She loves the fur type stuff. Several genes are known for structural types. We now have evidence that the Japanese Bobtail has a different mutation than the Manx, but there is something else out there, too, because the American Bobtail and the Toy Bob do not have tails that are caused by the Manx or the Japanese Bobtail mutation, so there's yet another mutation out there that is causing their tails to be short.

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In breeds, we know there are about 13 genes with about 15 different mutations that cause diseases that breeders should be monitoring, but there are lots of other diseases that we find in domestic shorthairs as well, and so those mutations are known also.

How have we been finding these genes? When we first started working with the Winn Feline Foundation, we would pick a gene and hope we were right, and that's called the candidate gene approach, and so we try to look at information from other species, and they give us a clue as to what the possible gene could be for our disease or trait, so that means always, always, whatever I do depends highly on the skill of a veterinarian, so if the veterinarian isn't doing a good job telling me what the pathology is of a disease, then I'm just lost in the dark, so the better diagnosis I can get, the better I can hone in on this candidate gene approach, so that's why I've loved working at a vet school. It keeps me tuned in with the veterinarians that are learning and creating the new knowledge and also gives us lots of good ties with colleagues around the world to be able to do our studies.

What things have already worked by just a candidate gene approach? Well, the early ones, back in the day, when Henry Baker found the ones for the Korat, the GM1 and GM2. That's because we knew gangliosidosis in humans. Here we've got the exact same presentation in a cat, let's sequence that gene in the cat, and lo and behold, that's where the mutations were. Back in the 90s, when the first mutations were being found in cats, that's what was being done. Gangliosidosis 1 and 2, the mucopolysaccharidosis that University of Pennsylvania works on, porphyrias. This is how we found blood type, and then many of your coat color genes, because all those coat color genes are first found in mice, and then we say "agouti! Let's go look at the agouti mouse!" and, sure enough, that's where we find the mutations. It doesn't work all the time, so notice I don't have dilution up here. That's because there are about eight different ways you can make a dilute mouse, and they look the same. They're blue, they're grey. You had to actually work through it to figure out which one to look at first and, in the end, it's melanophilin but, sometimes they work out, and sometimes they don't. Many of our diseases, one of our most recent ones we found is myotonia congenita, which actually was found in Burmese cats, now that I think about it, out of Canada, and it's also found, have you heard about fainting goats? That's what myotonia congenita is. The cats don't really faint. The goats actually don't faint, they get stiff, they can't get their muscles to relax, and so when they get frightened, their muscles contract, they can't relax, and they kind of fall over. So, just to show you, here is the blood type, so now, actually, we know B blood type, and we know the AB for Ragdolls only, so there's probably going to be more than one way you can make an AB cat, but it's very rare. Anyhow, Ragdolls seem to have one of the higher frequencies of it, but that paper just got published by Dr. Gandolfi. It was easy, it was an enzyme in the pathway to put these sugars on the end of your red cells, and so when the Italian student came, and she wanted to work on dog stuff, and I said "Yeah, but you've got to work on cat stuff," she just read the literature and said, "That's obviously this gene!" and I said "Go for it," and within eight months, from showing up at the door to the end, we had the blood type mutation. Sometimes it works easy that way.

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Other types of studies, we've had to do family-based studies. Remember back in the day, I was asking for parents and grandparents, and give me 5 mL of blood from everybody, and we had to keep building up the pedigrees and make them very extended, that was called linkage analysis, a family-based linkage analysis, and it often took a lot of time, because we had to collect all those individuals and stuff, and we had to have hundreds of genetic markers. We didn't even have genetic markers when I wrote the first grant for the Winn Feline Foundation so, in the meantime, we had to develop those genetic markers, and you really need to know the mode of inheritance as well, and so now you'll see that we're starting to be able to get a little washy on our mode of inheritance and still be successful with some of our studies. One of the big ones that worked this way was for polycystic kidney disease at Davis. We had a couple of clinics where we scanned 200 cats at a time and built up the pedigrees, had a pedigree with 100 individuals in it, and we genetically typed the markers, and we can see that one marker is always segregating with the disease, and why did we do it that way? Because there were four different genes known in humans to cause polycystic kidney disease. Why didn't we just do the candidate gene approach and go after PKD1? Back at that time, we didn't have a lot of sequence, so it was hard to analyze the sequence in another species, and PKD1 is a really big gene. Actually, all four of these are very big genes, so we could've been spending a lot of time just spinning our wheels and, of course, you have to try to do the best approach that you can, or at least the most scientifically sound approach. In the end, we found linkage to PKD1, we sequenced that gene, and we found the mutation for polycystic kidney disease. Other studies that have worked using a family-based approach was both the Abyssinian studies for their inherited blindness, spinal muscular atrophy, that's in the Maine Coons, and even some of the coat colors were done by linkage studies, but now we're in the day of case-control studies, and that's what we're always talking about now, buccal swabs. There's enough DNA to do a case-control study, so we're very happy about that, so just the amount of DNA you can get from a buccal swab. So, if anything, you should always be doing buccal swabs on your cat. Do a buccal swab, put it in a paper envelope, put it in a drawer somewhere. Make sure you mark it very well, which cat that was. When that cat later dies of heart disease, you already have DNA sample on that cat. Every kitten you produce, you should be banking, because, maybe the cat doesn't get sick; I need a control. So if you have a case, you need a control. A control of an affected individual is their normal sibling, or their normal parent - that's the perfect control for a case-control study. We don't need extended pedigrees. We can do things with a lot smaller individuals but, to make up for having less individuals, you have to have more markers. Well, we do have thousands of genetic markers now and, actually, the mode of inheritance you can be a little less sure about that, because you can analyze the data, whether it's inherited as recessive or dominant or incomplete dominant, so you can play around with the analyses a little bit and get around knowing the mode of the inheritance.

With the case-control studies, prior to being able to do case-control studies, we did all this population study work. You have heard me talk about the breeds, and how genetically distinct they are. Actually, we do know there's about 8-10 different, what I would call racial populations of cats from around the world. Europe is one of them.

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Europe is now actually split into the Nordic region and the Iberian Peninsula; cats from Spain and Portugal. Their feral cats now are different from the cats running around the rest of Europe are different a little bit different from the cats of the Nordic region. The cats of the Mediterranean are a little bit different, but the biggest difference is East, Western European versus Southeast Asia. That's a big, big genetic difference between those cats. We've been able to use this, and so when we made our DNA chip, we used these individuals, so these colors mean different groupings of cats. We used this information to help make a very robust DNA chip by picking cats from these different regions. We want good genetic diversity on our DNA chips. We want it to work in all breeds, so these population studies helped us to work on our health studies as well. We've gone up to maybe about 30 breeds now, and we didn't do all breeds, because we knew a lot of breeds would be similar, because they're just derivatives of one another, and one example is, genetically, one of the first things, when I got involved in the cat fancy was, I got called up to the office in New Jersey, and I was asked, "Is a Persian and an exotic a different breed?" and my answer was, "Whatever you choose it to be is what you choose it to be." But, genetically, no. Genetically, when there's only one gene difference; long hair versus short hair, or just a couple of genes' difference, that is not enough genetic difference for me to detect in any way, so I want to know that, because I want to know, can I use the exotics as controls in my studies of Persians, and the answer is yes. You, whatever you want to do is whatever you want to do, but we are finding that British Shorthairs have a lot of Persian in them now as well so, really, I couldn't tell you the difference between an exotic and a British Shorthair, because they're both short-haired. I can tell the difference between a Persian and an Exotic - one ought to have long hair and one shouldn't - what you do with a long-haired exotic, I don't know about that. Then Scottish Folds have a lot of Persian in them as well, but most of the other breeds, see their different colors, sometimes it doesn't show up so well, but we know that Burmese, we know that Australian Mist uses Burmese. Havanas are basically just a solid chocolate Siamese, and we know we can pick up the Aussie cat in the Abyssinians, so we know it works quite well on Korats and Birmanians are actually quite close to one another, one being long-haired and pointed and one not, but they're both Southeast Asian cats. We did prove that many cats come from where they say they came from, so the Southeast Asian cats are most closely related to populations of Southeast Asia, such as Korea and Vietnam, and so all the Southeast Asian cats do group down there. This bobtail -see there's no number on there? That means there's not a lot of support for the way we drew this evolutionary tree. The bobtail tends to move around. We now know the mutation. We know it's the same as the Karelian Bobtails, so we know the bobtail mutation came from the Far East, but it must have some type of a lot of influence from the West, because we can't place it strongly as a Far Eastern cat, and Menotti-Raymond's study said basically the same thing, and Abyssinians, they're kind of in the middle somewhere, so I'm not quite sure where to place an Abyssinian. They're not Western European, they're not Southeast Asian, so they're kind of somewhere in the middle; India, somewhere around there. Most of our breeds, though, do come from Western Europe. The Turkish Van, Turkish Angora, Egyptian Mau do tend to cluster with Mediterranean cats as well. Egyptian Maus are not from Egypt but maybe more new ones will be but, historically, they're actually not from Egypt, so I'm sure people are trying to get them out of Egypt.

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This led us to this study, where we said the darker bar is observed heterozygosity, and notice, if we had feral cats on here, it would just be this and higher for feral cats, so I just cut it off to the breeds, and so we can see the breeds that are getting lower, so one of the lowest is the Singapura, and then Burmese is right there with you, and Sokoke, but that really hasn't established well as a breed. That's not good, having low heterozygosity. The lighter bar is an inbreeding coefficient, and so you don't want that high. You want that to be low. If you have low heterozygosity and high inbreeding coefficient, that's not so good for you. We want to try to push those types of breeds to be thinking about outcrossing programs, and I certainly hope the CFA will help facilitate that and everybody works together to develop rules and regulations that allow that to happen, but this is where we did a study on Korats. It can be done. Korats have pretty good diversity, very low inbreeding, and it's why? Because they've managed their disease genetically. Remember they had the first ones known – gangliosidosis. They have pointed cats they don't want. They have cats of the wrong color they don't want, but they've always brought in imports, and they've always shared their cats around the world. They're a very low-number breed. Fifty, maybe, per year, and they still have very good genetic diversity, so you can manage your cats properly if you just all work together and do it, and so it might need some outcrossing programs and stuff, but recently the Abyssinians came up, and I didn't actually realize, just because where they were, yeah, their inbreeding is a little high, and their diversity is a little bit low as well, so now speaking with the Abyssinian breeders about their health program as well.

This is a DNA chip. It's just about the size of a microscope slide. It's a little piece of metal, and on there, they imprint 63,000 different little pieces of DNA that are the DNA markers that you are trying to test, and so one chip will have 12 different regions on it, so you can test 12 cats at a time, so now my life is always thinking about 12 cats at a time. I always have to have 12 cats because I can't re-use this chip, I have to do 12 cats. That's the instrument. The instrument is no bigger than this table or so. So, now we do our case-control studies on these DNA chips, and the data you get back looks like this. This is what we call a Manhattan plot, because it's supposed to look like skyscrapers, and what you want is the peak of Dubai. You want to a Dubai tower in your data, and so this was actually the first study we did, it was hypokalemia from the UK in Australian Burmese, and we did very few cats, 35 cases and 25 controls. We tested how low could we go, and we found that we could get as low as using 12 cats, and we would have got a significant..., so you have to test for significance here. This is certainly significant. Every one of these dots is a different DNA marker, and these are all the markers on chromosome 1. Chromosome 2, 3, 4, 5, and so you can see here, boom, that's where we look, so now you go and look, and now you go back to the candidate gene approach. You know where it lives on the chromosome and where it is, what genes are in that region that affect potassium metabolism. Well, actually, there was one for hyperkalemia in humans called WNK4 so it affected metabolism of potassium but made it go too high, so it's actually a good gene for analyzing for blood pressure and, sure enough, that's where we found the mutation. Now, we can do things much quicker, much cheaper. One chip, this analysis, costs about \$124 per cat. That doesn't count the part where you're actually having to analyze the data and then go look at a gene and the personnel cost, but you can get somewhere pretty quickly in a few thousand dollars now, if you have the cats, if you have the DNA samples, if you have the buccal swabs. Just buccal swab everything!

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We also did the Cornish Rex, and so gene on chromosome 1, and this was interesting, because this was only 11 cases. Remember, all Cornish Rex are fixed. Who is my control? I've got cases, they're all fixed for being curly cats. There are no straight-hair Cornish Rexes. That's where we used our population data, and we found the next closest breed, and one of the next closest breeds, actually, was Peterbald, and so we can genetically look to see who the next closest breed is. We used those as the cases and controls, and we found the mutation in this gene that actually causes humans to have no hair and to have poor dentition as well, so it's an epidermal dysplasia gene in humans. We all have the same genes, just what that gene does in each individual is a little bit different. We're still going after many of the rexoid breeds, and Dr. Gandolfi is knocking these off one by one. Our most recent one is, I'll show you in a minute, the Lykoi cat. What has been effective by doing these case-control studies? Already we've found hypokalemia, several of the mutations for hypo- or atrichia. Hypotrichia is the Cornish Rex, you don't have all your hair, but you have most of your hair, so it's low hair. The Birman gloves we found this way, and also the Burmese craniofacial defect. The Burmese craniofacial defect was a long, long-standing project. That's one of the first grants I wrote. The first grant I wrote for Winn Feline Foundation was called "Craniofacial Defect and Looking at the Genetic Diversity of Havana Browns," and both these projects have stuck with me my whole life, and so it started with Havana Browns, and now I'm trying to find cats in the Ukraine, and cats out of Russia to compare to, and I had one of the Ukraine breeders write to me, and I said, "Can you help me get cats out of Russia?" and she goes, "You know, we're not too keen on the Russians right now," and I said, "Yeah, I know, but I thought maybe you just might have a friend over there that, you know, wasn't involved in all this." We're trying to get cat samples out of places, and now that we see more cat breeds coming out of Eastern Europe and out of Russia, we're starting to see new colors, new health defects, all kinds of new, crazy things, so am I going to retire? Well, no, if there are more cats coming out of Russia, there might be more things to work on, but always, I need the base population information.

Just to remind you, the craniofacial defect, this was the beginning of it all. We didn't have genetic markers, so first we had to develop genetic markers, we had to build up these large pedigrees, and there are a lot of people that really stuck with us. Joanne Arnett and Karen Thomas continue to always help us with this project, and other people came and went, so we appreciate it. The traditional breeders were needed as much as the contemporary breeders, but it does cause an autosomal craniofacial defect that causes this duplication of the upper maxillary, but when you have one copy of this, you have the pretty little face that you want, and that becomes a problem. This is not new to animals, so in horses there's something called HYPP, which is a hyperkalemia periodic paralysis. That's in quarter horses, and the thing is, when you have one copy of it, you have big strong muscles, you're a good quarter horse. When you have two copies of it, then you tie up when you're a horse. So, selection of a heterozygote is nothing new. We know it happens and, in this case, it happens in the Burmese cats.

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Sometimes, these case-control studies fail, and that is because we might not have DNA variants in the right place across all the chromosomes in the right area that we need to look or, sometimes, your mutation is so old, there's no what we call linkage disequilibrium around it, so it's a very old genetic mutation. When we tried to do the Japanese Bobtail mutation, we could not find it by doing this case-control study so, in the end, now what the heck do you do? We've thrown all the tools we have at it. Well, there's still whole genome sequencing. Just so you know, Japanese Bobtail, they have these little hemivertebrae at every little kink of the tail, and so they can have all kinds of tails, either as a heterozygote or a homozygote. Cat breeders have certainly selected for the nice little bobtail that they want, but here was a cool secret that we found out, one that we radiographed the whole cat, because we just were looking at the whole cat, and the radiologist said, "Hey, wait a minute!" and we're missing one of either a thoracic or, sometimes, a cervical vertebra in these cats. So, Japanese Bobtail cats have, generally, one less thoracic vertebrae and so, sometimes, the ribs get a little confused to where to go but, in the end, it still looks like a normal, long cat. You wouldn't know that it's missing one of its vertebrae, but that becomes a very important gene for being involved with the development of your whole mammalian body plan. Who would know that? So, in the end, nothing occurs with these Japanese Bobtails, but it becomes a very important mutation for biology in general.

If you can't do something by case-control study, what are we left with? Well, let's just sequence the whole darn cat and see what we can find in that, and so we launched something called the 99 Lives Cat Genome Sequencing Project. Well, it started out as 9 Lives – and that's what Winn Feline Foundation funded – but then we thought, well, you know, that 9 is not going to be enough, so we wanted to get up to be 100, and everybody has a 100 genome project, and I was like, "We've got to make it sexier-sounding, so let's make it the 99 Lives Project" and, sure enough, everybody decided to play together, so all these different investigators from different universities have sequenced their cats the exact same way. It's a public database. It will all get put into the public NCI. Healthy cats are just as important as unhealthy cats, so if you just want your cat sequenced, then we'll put it in there. I think we're doing an Aussie cat with Roger Brown, and I don't think there's anything wrong with his cat whatsoever. That's good - we need healthy variants in there to say, "These are not the DNA variants you should be looking for, because these are the healthy ones, this is in a healthy cat. Go look somewhere else for the variant you want," and I'll show you some success in some wild cats that we have done as well.

You don't need to worry about this, but this is how we're doing it. This is where, when I say I want back-up blood samples, so to whole genome sequence something, you need about 3 to 5 mL of blood to do that, so buccal swabs, we're not so keen on that. It can be done, but we would much rather not do that. We've made these DNA libraries and, actually, our lab doesn't do it, we contract with Washington University or the DNA Missouri Genomics Core.

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We use the same technology. The cats might not be at the forefront of genetics overall, but we get to sit back and watch everybody else make mistakes, and so I sit there, and I watch them make their mistakes, and I say, “Okay, we’re not going to do it that way.” The key was to get everybody to use the same technology, because then you’re comparing apples to apples all the time. We have a company that does the analyses for us and, as I said, NCBI is the government place where you have to put all your short reads, all your DNA sequence into, so it’s all going to any other researcher who can use this data as well.

So far, we have already analyzed 83 cats, and 74 were domestic. At the end, I’ll tell you about the wrap-up with precision medicine again. Fourteen different institutions and some zoos are participating. We found inherited blindness in a black-footed cat and, also, of all things, Pallas cats have PKD. Why is that funny? Because people thought Pallas cats were the progenitors for Persian cats for a while. Well, no, they’re not, but lo and behold, they have PKD too. That’s just kind of weird.

Right now, we’re doing an analysis, or we’re getting ready to this summer, where we have Birmans that are coming in from Sweden with restrictive cardiomyopathy. Dr. Dodman is going to tell you about his Tufts cats. Cornell has put about 10 cats into this project. Michigan, with Simon Petersen-Jones, he’s looking at another blindness. Some people are just putting in other cats. We’re doing another Burmese with feline orofacial pain. We’re doing a Toyger. Nothing’s wrong with the Toyger. Nothing’s wrong with the Aussie cat. We’re looking for Siberians with hypertrophic cardiomyopathy, and Nosferatu, which I just love that name, is a Sphynx. Nosferatu. That cat, I think, has HCM as well. Black-footed cats have amyloidosis. Lions have a type of vitamin A deficiency. If they don’t have vitamin A as they’re growing as young cubs, their skull doesn’t grow properly, which then presses on their spinal cord, and they’re done for, you have to put them down and stuff, and so a lot of big cats are getting in on the project, too.

What has been successful so far? We have found Persian retinal degeneration. We have found a retinal degeneration in Bengal cats, as well. The Scottish Fold mutation is now published and, unfortunately for Scottish Folds, we have been able to show that you can have one copy of the mutation and, I’m sorry, you still have osteoarthritis. Before now readmitting to that, while genetically, now I can absolutely prove it. Now it would be nice, what’s the next step just with white deafness. The next step would be, let’s take all the cats that we know have the mutation and cats that have mild and severe osteoarthritis, and let’s see if we can find, there are probably modifiers that cause it. Same with polycystic kidney disease. Most cats live to 14 and don’t die of renal failure from PKD, but there were a lot of cats that died at two or three years of age and had severe PKD. There are modifiers to these genes, just like any cat with a melanophilin dilute mutation looks grey, but we know Russian Blues, British Shorthairs, Korat, Chartreuse, they don’t look the same blue. Those are all genetic modifiers that tweak everything in our body, and then also, spasticity was recently discovered and, also, a group in France have confirmed that.

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So, with retinal degeneration, there are now four retinal degenerations known in cats, two in Abyssinians, one in Persians, and one in Bengal cats. They all present the same way; different timeframes, though. If you do an eye exam where you dilate the cat's eyes, you will see that you can't see the blood vessels in the back of the eye. They're there, there's just not a lot of blood flow, so you just can't see them so well and so, over time, what's happening is these are the photoreceptors, and we can see that they're degenerating over time. This happens to be the Bengal cats, so by 62 weeks, actually, there's just no photoreceptors there. Now, cats trick you. They think they're sighted even though they're blind, right? So, if they have one or two photoreceptors still there, somehow, they can still see. Best way to check it out is with a laser pointer. Don't try to put something in front of their eyes. They can sense and feel all that movement, but a laser pointer will very much help. Are there probably cats that have two copies of these recessive mutations and can still see and are older? Probably are, because our body is very redundant. Other genes take control and help fix things in our body - that's why we survive, but that ought to be the rare cases. Does that mean you should breed that cat? No, because the next mix of that mutation in another genetic background, that cat might have very severe retinal degeneration as well, and you can do this with electroretinograms as well, so very early, as five, seven, nine weeks with a Bengal cat, we could see that the biggest peak is the earliest time, but we could see it dropping off - by even three months of age, we knew these cats were going to go blind, but they acted perfectly sighted up through a year, and one of the cats that Barbara Gandolfi adopted, it was chasing a laser pointer for two years and then, suddenly, it was all gone.

With our 99 Lives project, first we did 9 Lives and we sequenced three trios of cats, because we had no other cats in the database. We're just starting from scratch, so we thought we'd be clever. We sequenced a sire that was blind, an offspring that was sighted, and a mother that was sighted, but she carries the Bengal PRA, so she's a carrier of the Bengal PRA. Notice they have bobtails and curled ears, white body and, our favorite color, silver, right? So, we thought, wow! We can get bang for our buck for this one group of cats. That's what you can do with cats - you can't get people to do that. I'm not sure why, but you know.

To show you the process we go through, so this is for the blindness. There are millions of DNA variants that you're going to find; 16/16 million that we found in these three cats. How are we going to find the one we want? Well, you use the segregation of the disease with you. You know that the male has to be homozygote, because he's recessive, and the other two cats have to be carriers, so you plug that into the computer, and you say, "Kick out all the variants that don't fit that type of mode of inheritance, and then, also, give me the ones that affect the protein in the most dramatic way," and sure enough, and then also, we did a case-control study with those cats, too, so we knew where to look. We knew what chromosomes, so we could throw out all those other DNA variants and, in the end, we had one that's called a stop-gain. That means the protein has been altered and actually shuts off, and we looked at that one, and that was the right one in AIP 01 that caused Persians to be blind. If that would have been wrong, you could see we still had a few to work through, but the problem is there are lots of modifier genes down here.

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These are mutations. These are the mutations that are going to regulate diseases so, fortunately, we had one that was on-off, just affects the coding part of the gene, where we're going to start finding ones that are harder, and we're going to have to sift through these other mutations. How do we get this number lower? Having more cats in the 99 Lives dataset, so if we have more normal cats. My plea to you guys is, let's get every breed represented in the 99 Lives data. National Geographic gave me the money to put every one of the racial populations in, so we have every one of the racial populations represented. Let's get every breed. Every breed, it costs \$3,000. Come on, you guys are good fundraisers. Get those raffle tickets out there and make some bake sales, and it can be any cat you want! A healthy cat is just as good as an unhealthy one. Of course, we want to look at health, too, so to try to get bang for your buck, maybe find a cat that has more than one goofy thing going on, but that's where we want to try to head. The better this database, the faster we can weed things down like this.

We did find this mutation as well, and this was actually one of the first ones that I worked on when I was at the NCI as well, so this cat is sitting this way because it has generalized muscle weakness. This is one of the presentations of spasticity, so it's in Sphynx and Devon Rex cats. Back in the day at the NCI, boy, I did free blood testing for a whole bunch of Devon Rex cats but, in the end, we didn't get very many cats that were affected. Well, what's kind of happening is, people that are coming new into the cat fancy, and particularly in Europe and Eastern Europe, they're not as good at checking out pedigrees as you all are, and so recently, this has been gone for a decade or more from the United States. Well, this has cropped up new in Europe, and so the cat that we sequenced was born just two years ago with spasticity, and it came out of Italy, and so we needed a fresh blood sample for sequencing, and we sequenced this cat, and sure enough, found the mutation. This is a DNA sequence, and we found the mutation that causes this trait for the cats. It causes what we call a splicing error. Exons want to splice together. There are introns in between them, and we don't really know much about what the introns do, but they're probably part of regulation, so it messes up the splicing, and so the gene gets all gets messed up. Where your nerves are, what it basically does, you need acetylcholinesterase inside your nerves, for the transmission of the signal. COLQ is the gene that we found the mutation is in, and that holds the acetylcholinesterase into the membrane junction for the nerves, and so with this kind of dangling around and not being held well into the nerve membrane, then that's why the cats get spasticity.

One of our newest things – have you seen the werewolf cats? I have to admit they're rather cute, or I don't know, it depends, is the Sphynx cute? I don't know. It's all what you love as a parent, and the thing is these are cropping up in different places, so that, as a geneticist, there's no way these are cropping up in different places being the same gene. We have been able to do a case-control study, and we have found the gene for this, but we have found there are at least two different mutations, so the cats found in Virginia have a different mutation in the same gene than the cats found in Tennessee, and then there are cats found other places too, and so we're still looking around for some of their mutations but, in the end, they basically don't have an undercoat and so, actually, we did a resident project, and so they have the top coat of hair. They also have this roaning, where one hair is black and one hair is white.

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The cat's black hairs can come in different colors, but they always have white hairs too, so that, in other species that's called roaning. They have this roaning type thing, and then, see how dense your hair is supposed to be? They don't have all the undercoat of hair. This is where cats have their top coat, but not the undercoat, where Cornish Rex, or the other way around, completely different genes, and that's how they present, so we know two mutations in the Lykoi cats now as well. So again, we did this – now, this had to start with a pedigree, because it's brand new, but what you do for case control, you pick the most unrelated cats of the pedigree and do a case-control study for them, and so we were able to find this mutation.

Next one is interesting. We found this by sequencing as well. It's called an auto lymphoproliferative syndrome. It's in British Shorthair cats. Every one of their lymph nodes just blows up and becomes gigantic, and the cats are just months old when this happens and, of course, the cat has to be put down; there's really no good treatment for this but, in a recessive condition that we had some ideas of what it would be in humans, and what we did is, we didn't have a lot of cats - British Shorthairs in Australia - this was in Australia and New Zealand. We took two affected sibs, sequenced those, and then we said, okay. In our data analysis, these two sibs are affected. They must share the same recessive trait. No one else, in our other 84 cats, no one else can even have that mutation, because it's rare, and by doing that we can track down, very quickly, and then you go back to the candidate gene approach, because you're not going to only find one gene. Then we went back and said, "Well, how does this present in humans?" There were a couple of different genes to look at and, sure enough, one of them was what we wanted it to be. This has been submitted for publication as well. Now we found this one so, again, this is frameshift, where it knocks the frame of the reading frame of the sequence out of place but now, look, this says 33,000 down here. Now, because our database is getting bigger and bigger, this modifier pile is getting smaller and smaller, so if I had to still look at 3,000 mutations, I'm not going to do it, but we're getting smaller and smaller, so that's good.

To show you some successes in some other cat populations, the fishing cat is here. We'll be looking at amyloidosis. This is a cousin of the Asian Leopard cat. We've also looked at the black-footed cat, and then the Pallas' cat is right here, is another, kind of in the same grouping as Asian Leopard cats, so we're trying to get every one of the felids also into the 99 Lives project, because zoo populations are just like a breed. They're a closed population, you can't keep bringing cats in from the wild and, sure enough, they get inherited diseases as well.

There is a little black-footed cat. Cute, isn't he? Yeah, he'll rip you a new one! We wanted to test all the cats. There's only maybe 50 cats in the United States, so we wanted to test all the cats to make sure who's clear and who isn't, because now we have to use genetics to manage this population, and I was like, "Can you buccal swab one of these?" and they just laughed, and I said, "Okay, pluck some hair," and sure enough, we can do a DNA test, once we know the mutation, we can use plucked hair, not shed hair, but we can use plucked hair, so they just plucked some of the hair out of the cat, and we were able to test it. It's a small African Wildcat. Smallest little guy. Very endangered. Very aggressive little monster.

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Then we have the Pallas' cat and, historically, people thought, oh, this is the Persian! Well, we proved that not to be true, but these cats ended up, and we did the same thing, who wants to sequence PKD1 in a Pallas' cat. Like I said, PKD1 is a big gene, so it's actually cheaper and faster for me to spend \$3,000, sequence the whole darn cat, and then we can do other things with that sequence as well, and look in the PKD1 gene and, sure enough, we found a unique, dominant mutation in the Pallas cats and, unfortunately, we're finding that, probably, the progenitor cats from Russia have this mutation and stuff, so this is going to have to be managed in Pallas cat population as well.

For whole genome sequencing, we've found Japanese Bobtail, the British Shorthair disease, black-footed cat, Pallas' cats, and then Niemann-Pick type C. This is a type of lysosomal storage disease. It causes a neurological problem, and this is exactly what precision medicine is about. We had a cat come to our hospital on referral. It had a neurological disease that they couldn't figure out. First they thought it was a shunt. No, it wasn't that, and the cat just wasn't getting well, wasn't getting well with any treatments, so it came to us for referral and had Neurology take a look at the cat, and so the final decision was it probably has some type of lysosomal storage disease. We need a liver biopsy to know which one. The owner no longer wanted to do anything more with this cat, so that's it, we can't do anything more with this cat to finish the diagnosis. I was like, "Okay, here we go, let's see how strong our 99 Lives dataset is." We sequence the cat. We know which genes are top lysosomal storage disease genes and, sure enough, a recessive homozygote mutation in this cat that we have not been able to find in hundreds of other cats. That's one of the things we do to test... is it in any other cat? So, we found through what's the precision medicine approach; you use your whole genome sequence to help do your diagnosis. Now, in humans, they can do this in about 26 hours, because they have all the databases all set up to do all the analyses and stuff. We can do the sequencing and all that in that amount of time. We have a good database. We just don't have the computing power to do it that quickly, so it took us several weeks to do this, because we had to wait in line, but it does work, but still, it's not going to work all the time, but I was very pleased with this, and this is submitted to the Journal of Veterinary Internal Medicine.

A project we're working on that we haven't been able to solve: Oriental Shorthairs that came from Italy with these cute little cobby ears. In the end, they also have this kind of domed head. They have this severe hydrocephalus, so their brain is very compromised. This is one of my favorite stories though, because the females that have hydrocephalus don't seem to be able to get pregnant. Carriers can. But the males with hydrocephalus, they can breed left and right! It just tells you, you don't need a brain [laughter]- but women do, apparently! Not all of them are this severe and, in fact, these cats are as cute as can be. A teeny bit clumsy; other than that, you don't know that there's anything wrong with these cats, actually, and look how compromised their brain is, actually. So we know where this gene lives. We've done a case-control study. We know exactly where it is. It's not a coding mutation, so that means I'm looking at modifiers all over the place. So, guess what, that guy got moved down a notch as far as priority.

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We are looking at, in Australian and UK Burmese, there's Ehlers-Danlos syndrome. This is also called cutaneous asthenia and other things as well, where they have really stretchy skin, and so now we're going to collaborate with people to look at this as well. We've sequenced a couple of these cats, but we have no case-control study to tell us where to look, so we're hoping, with the next analysis with more cats, we might weed it down a little bit more. We're looking for dwarfism in the cats. We know where this gene is but, again, it's not a coding gene, so it's a regulatory gene, and the thing is, this is going to be a novel cause for dwarfism. This is not near any known human gene for dwarfism, and there are still lots of undiagnosed blind people. There's lots of still undiagnosed dwarf people so, if we find this and have the gene, we can say, "Hey, go look in your dwarf people and see if that explains it."

Bengal PRA is a novel blindness gene, so we're working with human physicians to test their undiagnosed patients for mutations in the same gene. We still hope to look for progression of PKD. We haven't really moved forward on that so much.

Let's wrap this up. I think we're close to wrapping this up. So, in the end, these are the variants of the cat. Just a bit of a summary. I think, maybe, you might have more details in your handouts there of what some of them are - I tried to update them before I came here - but I want you to realize that our laboratory has found 36 mutations in 25 genes. That's been my 20 years of work, so 32 publications, and three different investigators, Rob Grahn, Barbara Gandolfi, and myself.

Newest things have been in the myotonia congenita. This is out for publication in British Shorthair. Finding spasticity was really cool. Bengal PRA is not submitted yet, because we have to prove, functionally, that's the right gene. Lots of different color mutations. As I mentioned, the blood types. Hopefully, blood type is up there somewhere. Recently, also, we worked to figure out that Asian Leopard cats, because Bengal people have selected for some of the colorations of Asian Leopard cats, sometimes, when you have an Asian Leopard cat, allele, its variants mixed in with domestics, you get a completely different presentation, so that's charcoal, is when you have an Asian Leopard cat variant at agouti with the melanistic mutation, the recessive mutation in domestic cats, so that combination will give you charcoal cats as well.

I just want to say, we have received, over 20 years, \$300,000 or so from the Winn Feline Foundation, which is about \$15,000 a year, but we have 32 publications out of that, and Winn Feline Foundation has helped to find 36 different mutations in the domestic cat.

Things that we continue to work on are, Dr. Gandolfi loves the hair types. We just sequenced a wire-haired cat as well. We're still looking at dwarfism. We know where American Curl is, hydrocephalus. Still always looking at silver but just, honestly, the problem is it's a modifier, it's one of those regulatory mutations, and so that just doesn't jump at the highest part of my list, when I have diseases to work on, but other things, we'd like to look at stones in the mouth.

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One thing that I haven't solved, or two things, really, are silver, and the lymphosarcoma in the Oriental Shorthairs. So we're still trying to solve those things. We have a new project on amyloidosis. We have kind of a resurgence of this, where we have genome sequence two amyloidosis cats for Abyssinian and two for Siamese. We know to analyze them separately. We'll also analyze them together, and then we also have black-footed cats with amyloidosis as well, so we're trying to do this by a sequencing approach but, always, if we can get more samples of amyloidosis, that would be very helpful, and then also trying to look at Ragdolls, where they have only one uterine horn and one kidney; not really sure what to call that disease, and a few other diseases are moving along as well, and we'll probably look at those mutations for FIP to see whether they are showing any true risk for FIP or not, as well.

Just to wrap up with project cost, whole genome sequencing a cat now costs about \$3,000; \$2,000 for the sequencing, making the library, shipping samples, and \$1,000 for the analysis or so. Humans are trying to get to the \$1,000 genome project, so we're getting close, so as human prices come down, our prices will too. No, this doesn't include personal cost, when we start looking for genes and stuff as well. Still, the DNA array projects are very useful as well, and so it's about \$124 per one cat on an array, and if we, say we're working with Burmese, we can probably get away with 15 cases, 15 controls. Now, note all the cats we've already done, we can use those as controls, so sometimes we don't need the control samples and stuff. So, this localizes the mutation, but it doesn't tell us what it is. The genome sequencing will find the mutation, but now you've got to figure out which one of those 16 million are the right one. So, you've found the mutation, you've just got to figure out if it's the right one. So, again, lymphosarcoma we'd like to look at. We haven't quite given up on silver. I know it's there and stuff, it's just hard to move it up on the priority list. We've looked at a couple of genes, we thought we had it, and we were wrong so, in the end, regulation is key. It's going to become harder to find some of these mutations, but we have a lot of great tools in our ability, such as, for example, orange. We know where orange is, but proving that orange is orange is still hard, but that mutation ought to be coming out soon. As mentioned, humans do this in about 26 hours, where critical cases, kids that you must solve the problem right away, come into the Critical Care Unit, they genome sequence them, and they can get a therapy back to these kids. It doesn't happen all the time. We're finding about 60% of the important mutations are actually in the regulatory region, so I, fortunately, I've been working on easy ones for some reason and been finding them in the coding parts of genes. Now it becomes a little bit harder. So, humans have the same problem, is that most of 40% of the time, they can find their mutation right off the bat. The other 60% of the time, they have to work pretty hard to find it. So, we look for the variation of PKD. The idea is to start looking at more complex things, like obesity and asthma and infectious disease and, just like the same thing in humans, but, in the end, how about behavior? I think it would be great to hear about behavior, because everybody wants to look at domestication. While wild cats are on the fractious end, our friendly breeds are on the nice and feral cats are someplace in between, but they kind of overlap. Can we find the mutations that make a wildcat fractious and make a domestic cat friendly as well, and so behavior studies are certainly at the high end of the spectrum for complex diseases, and where we would like to go. So, with that, that's the end, and I'm happy to any questions. [laughter]

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