FIC BRAIN Webinar Full-text Transcript

"An Alzheimer Gene Crucible in the Far Mountains of Colombia"

Presented by Dr. Kenneth Kosik
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Kathy Michels: Welcome everyone. This is the first webinar series -- of our webinar series for 2013. We'd like to welcome Dr. Ken Kosik. I'd like to -- and before he starts I'd like to thank NIDA for supporting this webinar series along with Fogarty and for the National Institute on Aging for supporting some of the work that Dr. Kosik will be talking about under the Brain Disorders in the Developing World Program: Research Across the Lifespan, and this will be focusing on obviously the end of the lifespan. So that's basically all I wanted to say. If anyone has any interest in the program and doesn't know about it already they can contact me after the presentation and also through the Fogarty website which is http://www.fic.nih.gov. So without further ado thank you very much and take it away.

Ken Kosik: Well okay. Kathy thank you very, very much. I also want to thank the Fogarty Institute, the National Institute on Aging, National Institutes of Health, in general, for quite a few years of support, and particularly to the Fogarty for I think recognizing the importance of some of the research I'll talk about in Colombia very, very early on. It's really been a very nice and long-term collaboration and funding support actually from the Fogarty, as well as the NIA. You see on the first slide is the requisite disclosure that I should do. And I'd also like to just lay out what we'll do for the next, maybe 50 minutes or an hour. I'd like to open this with a movie that will be about five minutes, and although I've been working on this project that I'll tell you about for over 20 years with Dr. Lopera in Colombia who I will introduce to you quite a bit during the talk. But really the -- the real public attention to this project has really only come in the last year or two and this began with a visit to Colombia from a journalist named Pam Belluck of the New York Times. And someone who traveled with her did the movie which I would really like to show you. I think it's very, very compelling and makes a nice opening to the presentation. So can we start the movie now please?

[Silence]

[Music]

[Speaking in Spanish]

Narrator: In most of the world a parent starts forgetting and the children begin caretaking. But in the mountain villages of northwestern Colombia there's a ruthless reversal. People are getting Alzheimer's so young.

[Bells and Noises]

Narrator: Laura Cuartas has watched four of her children get sick all beginning in their 40's. Laura and her children are members of the largest family in the world to suffer from Alzheimer's. They are victims of a single genetic mutation that has touched the lives of the lineage of 5,000 people. Now she's 82 and a widow. Her husband who had Alzheimer's died almost 20 years ago. With the help of her daughter Gloria she cares for the ones who suffer from the disease. This pocket of sadness and forgetting is tucked among the mountains in a region of Colombia called Antioquia. Here the genetic trail leaves no question about who will suffer from the disease or when. It's a place where families are just waiting for Alzheimer's to strike. Until recently this family's disease seemed isolated, with few scientists working to help them. One of the only ones who is there is Dr. Francisco Lopera; a neurologist who's been studying this family since 1982. Scientists used to think that this family's form of Alzheimer's had little connection to the disease that affects elderly people, but their studies show that the two are remarkably similar. And that this family might be the best hope for developing an effective treatment to millions of Alzheimer's patients worldwide. After almost 30 years of research they've begun an unprecedented project [background talking]. They'll test drugs on the people here who have the gene but don't yet have symptoms. To see if treatment can delay, or prevent the disease all together.

>> This is the place in the world where it's possible to do prevention therapy more easy than in other place because here we have many people with this affliction.

[Music]

Narrator: [Background talking] Laura's fourth affected child Carlos Alberto and his family are among those who are suffering from this disease. Carlos has been married to his wife Blanca Nelly for 23 years. When they were younger he used to serenade her on his guitar. But when he was about 47 the illness began.

[Speaking in Spanish]

Narrator: The guitar is gone. She had to throw it away. It upset him too much to know that he couldn't play it anymore. And the disease continues to get worse.

[Speaking in Spanish]

[Music]

For this type of Alzheimer's the symptoms evolve so rapidly that every sensation and function is gone within just a few years.

[Speaking in Spanish]

And it's even worse for them, because Blanca Nelly's family has the gene too. She and Carlos are distant cousins. At 41 she doesn't know what her future holds. Three of her brothers and sisters are in the early stages of the disease and her mother is in its final stages.

[Speaking in Spanish]

Narrator: [Water pouring] Already her mother has lived much longer than anyone thought because of Blanca Nelly's tireless devotion.

[Speaking in Spanish]

>> Niño, niño.

Narrator: For Blanca Nelly caring for them is what she wants. If Blanca Nelly herself has early onset Alzheimer's her three children will have a 75% chance of suffering the same fate. And for the next generation there doesn't seem to be a way out. Families are trapped by this illness. It strikes them so young. [Background Music] But now scientists hope this extraordinary extended family can help unlock some of the most stubborn secrets of Alzheimer's. Not just for suffers in Colombia but for millions of people around the world. So that future generations like Blanca Nelly's children can live with hope instead of fear.

[Music]

Ken Kosik: So I -- when I first started to work on this project maybe 20 years ago or a little more it was immediately striking that when we visited a large number of people that commonly suffered from memory loss it was quite striking that another Colombian Gabriel García Márquez -- a Nobel Laureate -- had written in One Hundred Years of Solitude, a book I'm sure you know about a little fictional town called Macondo where people also lost their memory. And I think it's striking how very often art will imitate life and life imitates art, and the way these things go back and forth is always very poignant to me because there is -- although Márquez knew nothing of this family the resemblance is sometimes rather striking in his story. Márquez actually does have Alzheimer's disease now which makes the irony even greater. So we -- as you heard from the film clip here what was discovered back in the 1980's by Francisco Lopera, was an extremely large family in which dementia was inherited through many generations in what appeared to be an autosomal dominant pattern, and that was inferred from putting together many family trees and looking at the inheritance pattern. You see a few of these families on the slide right now. Putting together these families and by looking at who was affected it was possible to conclude that there was about a -- that the pattern was autosomal dominant, about 50% of the offspring would have the illness. At that time we didn't actually have all these families connected. They had similar syndromes but their relationships were still a little bit unclear. However, the tree consisted of about 5,000 individuals. We call them a family because we do know that they're family now since they all share the same rare mutation which I'll talk about in a moment. But at

that time we began to realize they were a family even though their relationships were at the level of fourth, fifth or sixth cousin. Now you can also see from this slide that the families in this region of Colombia, many other regions too are very, very large. It's not uncommon to have 10 or even 15 children so that we can actually see that the population has grown rapidly and there are large numbers of affected people. As I mentioned at that time although we suspected there was a gene we didn't know it for sure. Although we suspected the condition was called Alzheimer's we did not know that for sure, either. Really was -- it took a number of years until one individual finally came to post and the disease and the condition here was proven pathologically to be Alzheimer's disease. So we have this large family and it was a number of years later that the mutation was first identified -- and let me go to that slide. So in collaboration with Alison Goate, myself, and Francisco Lopera found that this single nucleotide change in the presenilin gene resulted in a missense mutation causing a glutamic acid at position 280 to change to an alanine and this was present in a number of individuals. It was really shown quite conclusively that this is the cause of the mutation for the disease that was presenting there. Clinically this looks like a textbook Alzheimer's disease except for one thing. The age of onset is very, very early. These patients begin to develop memory loss in their mid-40's, a condition we've come to call mild cognitive impairment (MCI). They transition to Alzheimer's disease at around age 49 and they actually -- which I'll talk about later -- even before age 45 have -- often have subjective complaints of memory loss even in their early 40's or late 30's, which we increasingly believe is a precursor to the onset of symptoms. So over the years from the early -- from the mid-80's when the family was first discovered to the early-90's when I began to collaborate with Dr. Lopera and then in the ensuing years we established the presence of the mutation and the diagnosis of Alzheimer's disease. Now I want to just introduce you now to just a little bit of the geography of the region so you can sort of understand the origins of this mutation. And the -- what you're looking at here is this very mountainous area. It's very beautiful, intensely green, with deep ravines, the mountains and a lot of forests. It's -- there are coffee plantations in the area. That is one of the major economic resources. And the population there consists of what we call admixture; that is a mixture of the indigenous Indian people, the Amerindians and the Spanish people who invaded the area beginning really with Christopher Columbus in 1492. I'll say a bit more about this in a moment but I want to just point out here that if you look right here and look at -- if you can see my arrow, right here is -- this is called Darién

Bay. And it's probably the case where Darién Bay where the arrow is, is where a number of the Spanish conquistadors entered the country in some -- in missions that were a number of years after Christopher Columbus in the -- probably around in the early-1500's. A number of conquistadors, Spanish males came over. And if we jump forward only 39 years you have the founding of the first settler town in Antioquia, which is Santa Fe de Antioquia, and in a mere 39 years from 1492 until the founding of that town the Spanish were able to ingress in an amazingly rapid way. I -- you know, if you see the geography there you cannot help but be taken by the fact that to penetrate the density of the region, the forest and the mountains and form settlements in such a relatively short time is a really pretty interesting perspective on the -- what the conquistadors were doing…in their thirst to find minerals and gold. So we have that entry point and this is what that region looks like today. Darién Bay as you can see is labeled and then this further inlet Golfo de Urabá and in the lower panel -- in both panels you can actually see that even today this is a very heavily forested area which is not so easily penetrated. Now we're -- and as you can see on this slide here, here are some of the routes that were taken by the conquistadors as they entered through that region and settled right down here which I'll show you on this arrow right there; in Santa Fe de Antioquia. And then beyond that additional towns were formed. And the reason I'm saying all this now is because we now know -- and I'm jumping way ahead here now because we've now been able to get as many as 100 genomes on people that have this mutation and it is now very, very clear that there are markers around the mutation suggesting that the mutation came from a -- from the Iberian peninsula…from the Spanish invader and not from the Amerindians. You can also do some calculations of looking at recombination rates around the mutation and we've been able to determine that indeed the mutation of the time -- of the molecular clock that we can put on the mutation, dates back to the early 1500's. So we have a pretty clear genetic track here on -- about the mutation. We also have here from work done by Andrés Ruiz, whose name you see in the lower corner, another feature of what I referred to as the admixture of the population here. And as you see over on the left there is a steady influx of the Spanish invaders generation after generation who had offspring with the Amerindian women and we know this today -- the genetic story is very, very clear because for many of the people in Antioquia you can see on their Y chromosome or markers from Spain, and on their mitochondrion genome are markers for Amerindians. The genetics makes the history very, very clear. I should point out that there are also people in the region; in areas such as Choco where

there are a number of Africans settled because they were part of the slave trade that took place at that time, as well. So now I would like to talk about the specifics and take you on a little tour of what it's like to do this research on -- in Colombia and how we have worked with the population and the families now for quite some time. And what you -- the person you see here in the picture on the left is Dr. Lopera and what he does and what we've done over the years is to call together in family meetings the groups of the families who come here -- come in this case to a hospital in Medellín and we will begin to talk to them about the nature of this illness; to explain to them what is Alzheimer's disease; to talk to them about various studies that we would like to begin and how we may be able to help them both in a research way and also talk about possibilities for improving quality of life. I'd like to show this particular picture because you see something here that is typical of Colombia and unfortunately a little less common in this country and that is you see the -- a young girl holding her grandma who is suffering from Alzheimer's disease. And in Colombia where they're -- especially for these families who often come from the countryside, or often are very poor, there are no mercy homes, there are no assisted living facilities, there is no warehousing of elders. Basically the children are with the affected individuals throughout the entire disease course until death and there is a closeness that I think you see in this picture between the generations which is sometimes a little bit obscured I think among us where very often elders are made to be a little bit invisible unfortunately. So we now are going on a -- setting out on a bit of a tour. Many of the families who are affected with this condition, who carry the gene have migrated in from the campo, the countryside, and have settled in these barrios, the neighborhoods, on the hillsides around Medellín. These are poor neighborhoods that are very similar to what are called the favelas in Brazil. And where people have put up these shanties and where many of the members of the family are housed here. It's only a small distance outside of Medellín. It's easy to get here and we frequently will go to the barrios and visit with family members. And you can see here is one such case. On the image on the left you see our nurse Lucia Madrigal who is working her way down a small alley passage and will go into that door there and inside is a young girl who is caring for her mother in the bed there, now in a vegetative state, who's had Alzheimer's for about 10 years. This girl is only 17 years old or 18 years old and she has -- although most of the families are very large, hers is not. And she has almost single handedly been caring for her mom under these conditions for nine years already. These are some of the remarkable stories that we see there and I will show you more about this. And so again as

part of the tour here -- compressing a tour very much -- after collecting and visiting a number of families in the Medellín area where currently about half of the families reside we head out to the countryside to original capital called Yarumal where there's another large collection of families. Yarumal is about a, maybe a five hour drive out of Medellín in small winding mountain roads and you -- once we get there we again -- once again will call the families together and talk to them about our studies and answer their questions about the condition. And here we are once again in a small hospital in Yarumal where we are talking to many affected individuals and their family members. And in this particular meeting I was struck by a question that I got. This is a question that came from this individual right there. And he stood up and he asked me, he said, "Doc, is it okay if we marry our cousins?" And now we know very well that in these large families there is a lot of consanguinity and we -- I was -- when I was asked this question as a geneticist I had to say that I didn't think it was a very good idea. But then he responded by saying something that I could not answer. Which he said, "But doctor we have nobody else to marry." And that is very characteristic of the nature of living in these areas. That people basically don't move very much -- So I -- where I left off here I had mentioned that this gentlemen in the front asked if their -- it was okay to marry cousins -- to marry and that's typical of the situation there where people live in small villages and tend not to move around very much. So this is really the origins of a lot of the consanguinity. Okay, where we continue our travels -- and to just to try to point out to you how devoted the families are to really -- to research and to really making -- in trying to bring the projects to fruition for their own sake and the sake of their relatives. And indicative of that is this meeting here where you see this large family in the upper panel that has come together in a town called Sopetrán. And the reason I'm showing this is because this family actually lives on the other side of the mountain up there and they came across that mountain from a town called Morón on horseback to actually get there. And that is again, these -- the families are knowledgeable about what we're doing. We met with them frequently. Increasing awareness of the condition and the research that's going on and this has really resulted in them -- in a very high level of participation and a high level of confidence really in Dr. Lopera's dedication to the project. And okay, now we're going here to another story. The -- we're now going to travel in the opposite direction to a town that is out through these roads that you see on -- in this lower panel down here, right down here. And the -- this is a town that's -- right here is a town that's called Acanya . What -- one of the things we have implemented, that Dr. Lopera has

implemented in Colombia for the families is what is called a social program. The people are quite poor and one of the -- and we're trying to provide help for them. In fact one of the most moving things that I have heard down there is when -- often when the families are asked what can we do for you, what do you need, what kind of material things can we provide; the answer we most often get is diapers. Because they really have very, very little. In this particular case on this trip to Acanya there was a woman out there that had rather advanced Alzheimer's disease and she was living with her two daughters who have a 50% risk and about a couple years earlier we had delivered a bed out there when she became vegetative. Now the -- on this particular trip though she had died and we went out to Acanya to pick up the bed and bring it back to Medellín where we would deliver it to another person in a barrio called Manrique which you see up here in the panel on the upper left. And delivered the bed into a -- right behind these walls here just to -- right behind these walls into this room right here. Now the reason I'm showing you this is because I want to get -- give a little bit of a sense of what it's like to do this kind of clinical work in Colombia. You know in this country we have things like HIPAA and concerns about privacy. When you're in these little neighborhoods around Medellín there is a -- there's no such thing as privacy. What you're seeing here is we got back to the neighborhood about 10:00 o'clock at night, delivered the bed into the room that you see up in the upper left and this is a public event. You see people standing around outside the door on the right and inside you see people coming into the room who are to watch the delivery of the bed which was a big deal. And the people in that picture on the upper left; none of them are related to the family. They basically are here observing this. When you're in a neighborhood like this everybody knows everybody else's business and the -- and when you're talking about genetic disease like Alzheimer's disease, and a disease that has a certain amount of stigma attached to it, you know, this kind of intrusion can be really difficult, can be very hard for people. But it’s also a fact of life. It is really something that would be really a very difficult thing to try to change the ethos of this in any simple way. Even though it is very difficult for the people in these families who are actually often referred to by their neighbors or other family members as Bobo. Bobo in Spanish is what they call each other when they have the disease. It means stupid. The disease itself they call “bobería” which means stupid disease. And so that there is a stigma attached to it and that is something that we and they face all the time. Okay. Now we're continuing our tour and this time we're heading out to a place that I had wanted to go to for quite some time but Dr. Lopera would never let me go because it

was always a little bit dangerous out there. This is a town called Angostura and you can see as we're now heading out there, this is now about a year and a half ago when things got a little bit better and we can finally make a trip. That even today you can see in the picture the military person out in this area. But it was very important to get out to Angostura because this -- although this is a place that sometimes I think about as through the heart of darkness it is also a place where there are a very large number of families and may actually be the place where the founder actually came from. We're not sure but it's possible. And so Angostura was a very important destination for us and we first got out there about a year and a half ago. Here's Angostura, the town, the street. Up in the upper right hand corner you see Lucia Madrigal once again taking a blood sample and down below you see one of the patients taking a neuropsychological test. So when we did finally get out there and -- oh, one of the things that we often encountered is the necessity of working directly with certain non-traditional ways of approaching medical issues. Both through the church and -- which is a place where people do here and there turn to for solace of course. But also -- and in this picture we see the church in Angostura and they -- and here is Padre Marianito who is really someone who is worshiped by the local people in quite a large area of Antioquia who comes from Angostura. And so with them -- through the church, but more importantly, through another stream of alternative medicine people that are the curanderas, the healers and the brujas, the witches, who are also very involved in the care and treatment of people there. It's really impossible to do medicine in this area without being aware that you're working side by side with another whole group of people that have a superstitious approach to medical issues, and if you just simply ignore it you're not going to be very effective. It's important to know that people are hedging their bets and while they do accept western medicine, they want to be sure that they're not ignoring this more -- this other stream. So we have to be aware of that and we are. We call the people together. Here was one of our first meetings in Angostura where once again, we gather the local people and talk to them about the disease and now at this point you see in the picture here Pierre Tariot who's right over here and let's see if -- there he is. So Pierre is now -- about two years ago we have actually brought -- we are no longer just simply collecting families and samples, but through the effort of Eric Reiman and Pierre Tariot and a group at Genentech have actually begun to put together a prevention drug trial for this population and I'll tell you a little bit more about that in a moment. But at this point what we're trying to communicate is not just the nature of the disease, but to tell people about the

imminence of a clinical trial that can begin. Now but in this setting we were really out in the more remote areas. Still it remains that the ideas about this disease are really in some ways we feel we really must dispel a little bit. Ideas such as the fact, that you might catch this disease by touching someone who has the disease. Now we try to explain the genetics because another superstition that was very prominent and is going away now was that you catch the disease by touching a tree. But they didn't know which tree it was. And for all these reasons some people get it and some do not. I think there is now beginning to be more sophistication about genetics and I hope that will begin to take these other ideas that are really connect -- that are very often evoked when people get stigmatized and putting them away. So we have here the -- a meeting in Angostura and the other thing that Dr. Lopera has done is to form a children's group. As you know we said this is a large, large family with many, many branches and there's another generation who carry these mutations and will be affected at some point. So here we are gathered on the finca, the farm that belongs to Dr. Lopera with all of the -- this is the teenage group and we brought them together to discuss the issues they may have and talk about what all we're doing. All of the work we're doing that will hopefully help them. You can see right in front here is the girl there who I showed you earlier taking care of her mom in the neighborhood Santa Domingo. Okay, so we will move on now. Here's -- okay so I did -- I mentioned that there is a lot of consanguinity and for many years we were looking for a homozygote in this population. We thought for sure homozygocity must exist because there was -- because of the interbreeding and the large size of the families, but for many years we never found a homozygote. And we began to think homozygocity of the presenilin mutation, this dominate mutation was lethal. However, recently we did find a homozygote. The first homozygote which is indicated by the arrow, here, in this family tree. In this family the grandparent's generation there is the mutation. We know that. And then in the girls' parents' right here and here, these are relatively young people in their 20's that carry the mutation and the homozygote is only eight years old. The parents you can see are cousins and this young girl here is for whom we sought exemptions and medical permission through ethical committees to do something exceptional, which is obtain genetic information because of the exceptional medical interest and got approval before doing anything. But we now know that this girl is not only homozygous but we also have tested her neuropsychological and she is essentially normal. I've met her myself and she's a charming girl, she makes eye contact, she talks to you and I think that -- we don't know yet whether she's going

to get the disease much earlier than others, but we do know now for sure that at least in her case, homozygocity is not inconsistent with life. The fact that we don't see it more frequently means that maybe she has something that's protective which allowed her to survive and maybe others did not. I don't think we can answer that yet. Okay. So I now want to switch gears a little bit from the stories I've told you to talk a little bit about the research there, the clinical work. And this is a paper which was recently published by Natalia Acosta-Baena and you can see here something I mentioned before; that the way this disease progresses, the way it comes on you can see here that the disease begins, has a mean age of onset of 49 years old. It will -- there's about a 10-year interval until death from the time of diagnosis. That's about the same interval in this country. Of course the range is very wide here but the interval, the mean age is between diagnosis and death is similar in both countries. MCI begins at around age 44 or 45 and transition to disease occurs in about five years. And we have begun to identify a condition that might be called pre-MCI in which individuals have subjective complaints of memory trouble which as I say seems to be somewhat predictive. Now, because of this pattern that you see right here, that is a clear progression that unfolds like clockwork in most of the individuals in these families. The fact that we can predict by checking for the mutation who falls into these groups; it is this finding which stimulated the broader interest of the Alzheimer community to begin to think about whether or not the population would be appropriate for a clinical trial. I'm sure you're aware that if we go back maybe four or five years ago, maybe a little more the Alzheimer's field had its own kind of Challenger disaster in which the number of drugs that were in phase three trials all failed and there -- for some of the antibody treatments there were even some deaths. This drove people back to re-establish, to re-think exactly how we were approaching clinical trials. And what came out of these phase three failures costing literally hundreds of millions of dollars; they -- many major companies suffered the losses, the failures of these trials. Many years were invested and in the end the field underwent a kind of a shift in its thinking in which we began to think if we're going to have any effect on this disease at all we have to treat it before the disease strikes. And it was at that point when this thinking began to happen, this shift in the broader Alzheimer community that the work that Dr. Lopera and myself had been doing for many years in relative obscurity actually came to the attention of investigators, other investigators around the country. One of the first people to call me was Eric Reiman and Pierre Tariot who proposed a clinical trial. That clinical trial has actually been funded using a drug made by Genentech called

crenezumab, and if everything goes well we hope that trial will be launched maybe within this year hopefully. And the infrastructure for doing this clinical trial has -- is really already underway in terms of collecting people, collecting clinical histories, assembling samples and most importantly perhaps obtaining the biomarker evidence for the changes that are occurring pre-symptomatically. That is changes in PET amyloid scanning and done by Adam Fleisher and CSF markers for abeta and tau that are all being measured and they'll use these biomarkers as potential outcome measures. And that is work as I say that is being actively pursued both of -- at Genentech through the project leader there Carol Hough and through the Banner Health people. Okay now my own interest in here that I've continued to pursue is, the fact that while people transition through Alzheimer's disease at age 49 like clockwork, there are outliers and not everybody does. So we would -- have set up a genomics study to actually find age-of-onset modifier genes. To find out why it is that a small group of people do not undergo this transition. That their disease onset can be delayed by as much as a decade, or accelerated by a decade. It can go in either direction. And so that is a project that is currently underway, and you can see here that we do have a high heritability of age-of-onset in this population and a number of people -- relatively small number but a probably significant power to identify allele that may be shifting the age-of-onset beyond one standard deviation in a direction that's either deleterious or protective. And this kind of thinking, however, is based on an assumption that the shift in this curve is driven by a single allele. Now whatever this allele is, is very strong because the age-of-onset is just so tight, the mean age-of-onset is so tight around age 49 that for those people it's falling outside of that range there is likely to be a strong genetic modifier and -- but I say likely because there may be multiple alleles which will be harder to detect. There may be environmental factors that are changing the age-of-onset. Although, we don't think so because this population is relatively homogeneous genetically, in terms of their education levels, in terms of their occupations and diets, and the amount of exercise they do. All the things that can modify age-of-onset in Alzheimer's are not very variable in this population. So we have a good shot to find something we think. And we now have 100 genomes that we're looking at of people with the mutations. The first six of these were analyzed in a recent publication here that's listed at the bottom of the screen. The -- and I emphasize here that this -- what I'm going to show you now is really simply a way to think about how we would begin to look at this analysis. I really want to emphasize that with six people this is obviously not statistical data by any means. But it does

begin to show you some of the power of how doing genetics in this population, some of the power that we can muster to get information. So these six people had -- there were two with deleterious modifier, a punitive modifier who had their onset at age 40. Two with a mean age-of-onset in the late 40's, and two with a protective modifier. There's a father and son here as well, so you can see that even within the same family if there is a modifier allele it was differentially inherited from the father who apparently did not pass it on to his son who had the mean age-of-onset right there. So as we look a little deeper at this one of the things that we can do with these genomes and now the larger set is to actually lay them -- or lay out everyone's DNA and compare it pair wise between each individual. That is what you see in the perimeter of this circle here is the -- is right around the outside here are the chromosomes and the DNA is laid out in pair wise comparisons. So for instance this inner circle here is the comparison between the father and son. Now wherever you see a colored region that means there are stretches -- relatively long stretches of DNA that are identical between these two individuals. So there you see that and here's the region where they all carry the mutation. And there are other regions that look like they're all colored the same but I just want to point out that's sort of just centromeric regions that will have this as a kind of artifact. But this is real here where the personal mutation is and what we're looking for here, are regions where say like up here there will be two -- I'll just go to the next slide -- two individuals who both have -- say a protective effect and they share a stretch of DNA. So here's a number of individuals that share a stretch of DNA and let me show you one more slide; here we -- these individuals that are shown here have -- both have late-onset and they would have a piece of DNA that is shared between them and therefore that piece of DNA is a region which we could then go deeper and see if it holds up in other individuals and may contain a modifier gene. It's a way to limit the three million genetic variants between any two individuals even in this population, and narrow it down to stretches of DNA that are shared between two people that have the same phenotype. In this case a delayed onset. We call this technique Identity by Decent or IBD. And that refers to laying out regions of DNA that are identical in two individuals. Okay. Now -- let me just try and see if I can advance here a little bit further and -- sorry just having a little trouble moving and here we go. Okay. I want to take just one more moment. I know that the hours getting a little late. I just want to mention one more thing that we're doing here which helps us to get genetic information from relatively small samples of individuals. One of the other tools that we've developed is that we now have small skin biopsies

from a number of people that carry this mutation. And from those biopsies we can then -- as you know using the IPS technology that is making induced pluripotent stem cells; we can create stem cells that carry the genomes of these individuals. We can now take those stem cells and differentiate the cells into neurons and look at which genes are expressed and which are not. We can look at any changes that are going on in this expression profile, which we call a transcriptome by sequencing the RNA in these neurons. It's the only way we can get RNA from individuals that have these phenotypes without for instance doing a brain biopsy which would be obviously impossible. So I'm showing -- so we don't have that data yet, but I just want to show you one example of how this kind of thing works and here is a what we call integrated analysis of an individual that has a -- has another mutation; this is actually a case of a frontal temporal dementia. But in this case we're looking at a gene called ATP5SL and this individual has a polymorphism which changes a wild type nucleotide to a T. Now here's the point; notice where -- in this T, this site, this polymorphic site falls right in a spliced junction. So notice in the genome all we would know is that there is a polymorphism that changes one nucleotide to a T. But in the transcriptome we can see that wherever there's the mutation in the slice site there is read through out of the axon into the intron right there and I'm showing you. And that occurs only where you have the polymorphism. Where you have the wild type allele the axon ends appropriately right at the axon boundary. So once again the transcriptome can help us interpret the genome for showing those particular polymorphisms that are more likely to be involved in some sort of pathology. Okay now I'm just going to finish up with the last few slides here. And I want to make the point that we -- that this -- the familial Alzheimer's disease that I've talked about here, the E280A mutation in Antioquia is really only the tip of the iceberg. There are a number of dominant diseases in Antioquia which haven't even begun to be studied yet. For example, if you look up here there -- here's another mutation leading to Alzheimer's disease and presenilin. This is almost as large a family living in a town called Copacabana outside of Medellín. Hardly even studied yet. Two cases of Notch 3 mutations leading to Cadasil, which is a disease that causes strokes in, relatively young people. Again, two families here with these two different Notch 3 mutations. Families again, almost as large. And a number of other dominant mutations in this population. We're really -- we really have a kind of a treasure trove here of genetic issues that in which I think we can get insights that are actually very deep. Very similar to what we're getting in the Alzheimer's families. So the last thing I want to show you is then -- is

to address the question as to why we are having so many dominant mutations in this region of Colombia; Antioquia. It may be occurring in other regions too it just hasn't been studied. So what you're looking at here is what we call a disease map and the -- these red areas are where the Alzheimer's disease families live. The other colors are other genetic conditions such as Gilles de la Tourette and Cadasil in some of these other regions. Also, discreet areas -- geographically discreet areas with founders who are probably different individuals that left their mutation in these regions. Now the population of Antioquia today is 8 million people with a smaller founder population. How -- and we know when populations are relatively inbred you get recessive mutations and that does exist here. But why so many dominant mutations? This is a mystery and I will conclude by showing you simply a speculation on why that may be. Here are two other genes listed at the top here of the screen. There two genes that are associated with diabetes that have been sequenced over, and over, and over again, in over 13,000 people. And the number of polymorphisms that is found keeps increasing along this axis. If the population were stable we would expect that the number of polymorphisms that we would find would level off. But it doesn't. It continues to go up and this is characteristic of a rapidly explosive population. So one of the things that we think may be going on in Antioquia is that with the rapid population growth, there has been an excess of mutations that have occurred in the populations; some of them causing dominant diseases. Okay, and when you put all these different mutations together and indeed here we're looking at data from the Autism field -- when you put multiple wild mutations together you begin to get a genetic map of a disease which is something that I think we can do in this population as we go forward. So I'd now like to conclude here by going back to the original story I told you about Macondo from Gabriel Garcia Márquez, in which at the end of the chapter it turns out that in this village a gypsy arrives and he brings with him "una sustancia de color apacible," which means a substance of a gentle color. And when he gives this substance to the people their memory loss is cured. So with I hope that with what we're doing we will be able to follow in the path of this fictional rendition and have some sort of impact on these families. And with that I would like to have some -- make some thank you's. We have a lot of people involved here. Some people -- here's the Banner group with Eric, Pierre and Adam Fleisher. People from my lab at UCSB. We -- Andrés Ruiz; a lot of the genetic work, the genomes being done by -- in collaboration with people in the Institute for Systems Biology, including, Mary Brunkow. Work on people that you -- that some of you know; a former student of mine Joseph

Arboleda. And imaging work by Yakeel Quiroz. But most of all the person who really deserves probably the most credit just by far because of the tireless work he's done in this area is Francisco Lopera who has just seeing this first hand will go spend hours and days and weeks and months and years tirelessly going from village to village to collect these stories, to collect the histories, to do the neurological exams, and to make all of this happen. It can't be forgotten though that not only have we assembled various groups like the children's group you see down here, but in this upper image I particularly want to thank the Fogarty Institute for what you -- for this group which is the research group in Colombia that has really developed, that has built capacity at the foreign site. Because this is the group that has actually over the years and the grants that we have received from the Fogarty has actually allowed us to build a really solid research support group down there that allows us to encourage research locally as well, and to make this entire project possible because the people feel that they are directly involved in this research. So with that I will just show you -- one more time I will thank Dr. Lopera,shown right here, who is the man who stands behind all of this work. Thank you very much. Okay so to -- I see some questions that are showing up here now and I hope people are still hearing me. I'm going to read the question that is showing up here in the chat room. Here we go. What is the age-of-onset for E280E in AD patients outside of the study population U.S. and Europe? Well, so I think this mutation doesn't exist. This is a private mutation. It only exists in this population so we cannot really say -- determine the age-of-onset for this mutation in other populations outside of Colombia. There is a small family in Japan that does have an E280A mutation but it's due to a different nucleotide in that codon. And it's a very small family so we can't really talk about a median age-of-onset. And then the person went on to ask; besides genetics, environmental factors considered? And as I mentioned this is an issue that exists in every study, but less so here, because the people in this population are -- their risk factors are relatively homogeneous in terms of diet, exercise and education level. Okay, so I hope I'm not skipping a question here and let's see. Okay, how are the effective symptoms in this AD population -- the affective symptoms? So this is really textbook Alzheimer's. People become depressed, there's clearly later on they will develop some of the paranoia that you see. This you can really -- except for the early age-of-onset this is very, very much like the Alzheimer's that we're familiar with. Does the social support provide benefits? Basically not really. You -- the social support will provide -- as I say, the diapers, the beds, and a lot of some support services in terms of attention from nurse aides.

But actual financial benefits for the most part, no. Although when people participate in the research they are paid for time lost from work. Okay let's see, so next question is; what do you think are the main lessons in capacity building in Latin America that you can share with us? Great question. I would say to me the main lesson that goes, that is -- just goes far beyond every other lesson is that doing research in Latin America or any other place in the world must involve really a lot of participation from the people that live there locally. We have had a rule from the beginning that for all publications we believe that a person from the research group in Colombia, from the Lopera's group should be an either a first or senior author on every paper. They should have the opportunity to make an intellectual contribution that deserve that position on the paper and that we have to build capacity locally to make this kind of research happen. Okay, from the side of the patient population what are the benefits if any that this study has brought them? Well, the social program has brought some quality of life improvements I think. But I think what really -- we bring -- I have to be perfectly honest; I think what we bring is some hope that one of these drug trials will make a difference. I think there's another question here. So these -- here we go. I'm going to read this question. There are obviously many hurdles to establish research abroad and specific to South America. In Dr. Kosik's experience what have been the key points that have contributed to the success of the AD project? So it's really the same answers I said. The key thing is the involvement of the people locally. This is just a remarkably invigorating group of people to work with and I think it has to have local participation to succeed. Another thing I'll add on this part is that the participants, the families have extraordinary trust in Dr. Lopera. He comes from this region, his sister, his mother live in Yarumal. There is -- people know that he's from the same family that they are from, and they -- and his dedication is often having someone on the ground, like integral to the success of this project. Okay I think I've -- if I've missed a question please just maybe you can send it back in again, otherwise, I think we're winding down. Thank you all again. Okay here we go. I did get another question: Could whole genome sequencing in cancer and other diseases cause a confluence that can assist in the genetics to understand Alzheimer's for treatment? I think so. Because I think that it's remarkable how genetic maps and biochemical pathways tend to begin to overlap. That what we learn about cancer genes in terms of proteolysis and various pathways like that tends to spill over into Alzheimer's disease. There's just a remarkable connection emerging now I think in the -- which a number of compounds used for cancer that will attack the proteasome could be useful for

clearing intracellular aggregates in Alzheimer's. Also, how is your work related to the Obama brain mapping initiative? And that I think is still hard to say. Whenever they talk about the brain mapping initiative they always drop the word Alzheimer's. I don't think the connection is that clear at this point but I think knowing more about the brain can be helpful and I'm optimistic that the brain mapping project will offer insights. I think we just need to know a few more details and think about it a bit more deeply. Is it your expectation that gene therapy will be available in the near term? I don't think it's going to be available in the near term. And then I think finally just to close out here I see you can see yourself in the chat room that Kathy Michels has reminding everybody that the presentation will be archived and I welcome any further questions by email or contacting me in any way you like. So thank you once again for coming.

Kathy Michels: Thank you very much, Dr. Kosik, for coming, and thank you everyone for joining us.