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Please stand by for real-time captions.

>> This is Robbin Bull and I want to welcome everybody. And then I will hand it over to Pam Ryan.

>> First as you know all lines have been muted so you do not have to worry about part -- background noise. At the question-and-answer session that will occur at the end of the presentation however you can write your questions in the chat box at any time during the presentation. It will be monitored throughout the session in preparation for the Q&A session.

>> This webinar is going to be recorded and I am going to start the recording and once you hear the message that the recording has started then that will be pans queue to get started.

>> I'm starting it now.

>> Good evening everyone I have the pleasure of introducing our speaker for this evening Meg Hefner . This is Pam Ryan and as Megan is my friend and longtime colleague it is fun to be able to introduce her to something like this.

>> She is a founding mother of the The CHARGE Syndrome Foundation and she is our resident genetic expert and we depend on her to help us learn about this complex condition called CHARGE. Is a clinical associate professor at St. Lawrence University at the Department of pediatrics and in 2010 perjuring of eight transport specialty clinic became a reality [Indiscernible - muffled audio] children's medical center near St. Louis. She worked hard to engage physicians to work with her to develop the center of excellence where parents can go and get answers from professionals who make has nurtured and she also made them fall in love with charge -- CHARGE She is devoted over 30 years to CHARGE in her role as a counselor but as a guide also to family meeting answers to questions about their fragile children. In an effort to share all that she knew and continuing to learn she was the lead author of the first booklet for families as well as working with one of her colleagues in another founding mother of CHARGE our very own position in charge Dr. Dr. Sandra Davenport and they together produce the management manual for parents both of those things done in the 1990s.

>> The management manual updated in 2002. Meg was involved in defining diagnostic criteria for CHARGE use by medical professional and she was editor of the special issue of the American Journal genetics and in 2010 also was the lead author of the book known as CHARGE syndrome what we refer to as the CHARGE book . Tonight our friend will talk to us about the latest research being done about CHARGE and try to answer any questions you may have about this research .

>> Here is Meg Hefner and her presentation CHD7 and send it research -- syndrome research unveiling the mysteries. [Indiscernible - low volume]

>> I hope I am able to live up to your expectations.

>> I will be doing at this point -- talking about CHARGE research and where it is being done and what research is being done [Indiscernible - background noise]

>> Is the sound okay now?

>> I will be going through a lot of research things and I hope there was some type your questions at the end and certainly we will go through as much as we can and they're so much going on that it is impossible to cover everything in the time we have but we will go through a lot.

>> First where is CHARGE syndrome research being done and you will notice from the slide I have abbreviated CHARGE syndrome as CS to read through the slide more easily.

>> Over on the left-hand side of your screen you can see under files the webinar and that is the PowerPoint and something you will be able to download. The webinar will also be recorded and available at the website probably later this week if you want to review things.

>> Charge research is being done basically all over the world and I have looked at articles from the United States and Canada in many countries in Europe including United Kingdom and Netherlands and France and Germany and Italy and same and a lot of research is being done in Japan and really all over the world.

>> It is actually difficult to see where some of the research is coming from because a lot of it is collaborative studies involving multiple institutions and often in multiple individuals and institutions in different countries.

>> What kind of research is being done? Various kinds of human research being done and some of the reports in the literature are clinical case studies and observations. Some are a series of a number of people with CHARGE and some are summaries of observations and management issues. Clinical reviews that look at or take a lot of the literature and put it together in review and there is a lot of stuff on very specifically on CHD7 the CHARGE gene and its relevance to people and different aspects of CHARGE

>> There is human research that is not just observational but going and gathering information and some is observational and some is using questionnaires. And some of the really exciting stuff going on cutting-edge stuff is animal models. Both the animal models and the human stuff involves molecular research and understanding about that.

>> I will be reviewing some studies of each area including some of those that have been funded in part by the The CHARGE Syndrome Foundation . Far more going on that I could possibly cover tonight [Indiscernible - muffled audio] not covering everything that I read about or reviewing everything that is in the literature human or otherwise. But I will try to hit some of the highlights.

>> Caveat. I reviewed scores of papers to prepare this webinar and I really only went back at most re- four years. Older stuff is not included in this for the most part. So much available that it is really very new and exciting.

>> I am also not providing citations for everything I reviewed. I do have citations on the figures that I am using and that kind of thing but I will be showing new information that I gathered from probably 50 different publications and even so there is a lot I am not covering.

>> If there are topics that you want to hear more about let us know. Maybe that is just there could be a webinar in and out itself or when we are preparing for next summer CHARGE syndrome near Chicago we can invite people to present about topics that the people particularly are interested in.

>> Getting to the meat of things. First I will talk about is case studies and in the medical literature a case study is typically a report of a single case or a few cases and these are used to talk about new features or a particular management issue and things that came up in a particular case that maybe useful to people in other situations and one example of a case study that is not actually out in the literature yet is from colleagues and I looking at craniosynostosis occasionally finding charts and. That is premature closure of the sutures of the head and it distorts the shape of the head and usually needs to be treated with surgery.

>> I have known for a long time that is an occasional feature of CHARGE but it was pointed out to me that that has not been reported in medical literature and others do not know about that . So through finding people in the my CHARGE database and the Facebook pages we have identified eight or nine kids with definite diagnosis of CHARGE syndrome who have craniosynotosis. And this is important to report because in at least three of these cases the diagnosis of CHARGE syndrome was actually delayed because the medical geneticist evaluating these children was looking at the craniosynotosis syndrome.

>> And this means some of the features they should've been looking for and managing and related to CHARGE were not looked at quite as quickly as they would have otherwise.

>> And it is just important for everyone to know that can be an occasional feature of CHARGE if you have craniosynotosis then that does not mean it cannot be CHARGE. But still can as I'm sure most of you parents know ready much anything can be part of CHARGE.

>> Every year I learn more and more things [Indiscernible - low volume]

>> Some of the other case studies I came across came about -- talked about publications that have been seen with children with CHARGE. One was a report from Germany on a six-year-old child that has his tonsils out and tonsillectomy is a surgery where there is a really high risk of some bleeding and this child had some very excessive bleeding that lead to aspiration and bronchospasm and actually needed to be resuscitated.

>> He was successfully resuscitated and he was okay at the time of publication of the paper but they were pointing out that with the exception leading you can have aspiration in these kids and it is something to watch out for.

>> Another report I came across up was from Japan and this was a child -- part of CHARGE syndrome -- let me put the phone right in front of me. [Indiscernible - background noise]

>> Trying to get my sound good.

>> In Japan there was a four-month-old child and part of his CHARGE syndrome had severe immune deficiency and one of the ways they treated that was by a cord blood transplantation.

>> And that was successful and it did not completely cure him because he had sinus abnormalities related to the immunodeficiency as well but he is doing much better.

>> Other case studies look at CHARGE syndrome and compare it to other syndromes and all of you know that CHARGE has features that overlap with many other syndromes and actually when we get to some of the animal models and molecular things at the end of the talk we will see part of why that is.

>> But a recent report from the Netherlands was the group of people who identified CHD7 as being the major CHARGE syndrome [Indiscernible - muffled audio] they reported five children to from the literature and three that they had seen who have a chromosome 5 micro deletion [Indiscernible - background noise] heart defects external ear abnormalities and

>> -- Short stature and those are obviously things that overlap with charge -- CHARGE features and none of these children had Kalevala was or [Indiscernible - muffled audio] abnormalities or lack of sense of smell. And that is part of the reason why those are some of the major features in the diagnostic criteria or CHARGE is -- not because everyone with CHARGE has them but because they are so rare in other syndromes it helps to distinguish.

>> Another study from the French study looked at pituitary abnormalities in CHARGE syndrome and this paper summarized some of the pituitary abnormalities that have been described in CHARGE and children with Coleman syndrome has pituitary abnormalities and lack of sense of smell and so there is overlap with that.

>> They actually had some children with Coleman syndrome and they had familiar locations of Coleman syndrome and tested them for CHD7 and what they found [Indiscernible - background noise] variance in CHD7 not one that they could say for certain our abnormalities but they may well change the way the protein works in a way that only gives you these features of common syndrome and we are not sure. Shop and then there is another report from the Netherlands on eight reporting a child with kabuki syndrome and has CHARGE syndrome features and in particular call Obama and pituitary issues.

>> I actually personally follow the child for many years with the diagnosis of CHARGE clinically bit charge but she never had the phase and her ears were little different and she turned out to have kabuki syndrome and then I found many other kids who have kabuki syndrome with many features of CHARGE so again there's a lot of overlapping their and we will talk about that a little bit more later on as well.

>> Again recognizing there is overlap and diagnosis can be confusing and if you have a child that clinically that's a syndrome but does not appear to have the genetic basis of that syndrome consider other syndromes that have similar features.

>> Another thing that goes on our series. These are looking at many people with CHARGE syndrome and saying you know what are we see with them?

>> So there was a paper from Italy that look that eight children with CHARGE syndrome and looked at all their dental findings and there were lots and lots of findings that they did not see any clear habits and that. That is still a very useful type of publication because it said okay this is what we have so far.

>> When other people look at more children maybe from -- some patterns will emerge. Another study from Japan looked at 19 children and look at their eyes so they look at 38 eyes and the 19 children and they found pretty much would you would expect as far as color bombers and some micro family it which is a very small I.

>> There were things that were in use and will not necessarily new but really helpful to see is that there was a lot of asymmetry he cleaned the two eyes so often time there was a coloboma in one eye or when I was small and this is something that we see in a lot of CHARGE syndrome is that the two sides are not like each other.

>> No matter what it is there is a lot of asymmetry. And something that I found very helpful is that they said that even and I with a large call Obama can form a macula. coloboma Is a disruption in the way that retina is formed and that is what gives you the huge blind spot and the visual field defects that we see in CHARGE syndrome .

>> A lot of children were CHARGE have legal blindness by virtue of a very small visual field and get a lot of family say all but my child can pick up eight piece of lint on the carpet and can pick it out while that is the macular vision and the central vision and the detail vision and even with a large coloboma there is a functional [Indiscernible - muffled audio] and that is awful because when your babies were little you were told that your child will be blind and from a legal definition of legal blindness many of them are and yet many have some very functional very usable vision where ever their vision is and it may be good and this confirmed that that can certainly be the case in many children with CHARGE.

>> Another study from New York City look that temporal bone venous malformation these were 18 children that were being evaluated for possible cochlear implants and they were doing MRI to look very carefully at what is going on inside and what is going on especially with the blood vessels. Of those 18 children 10 of them had blood vessel anomalies in the area where surgery would be done.

>> This clearly has very significant implications for possible surgical complications. So knowing where everything is is really important before a child has surgery.

>> Speaking of cochlear implants there were a number of series reported of cochlear implants and this look that -- three kids from New Zealand and 13 from Germany and six from Korea and five from Italy so for different papers. That there were some common threads in these reports.

>> The common thread is all of these children have complex middle and inner ears. And I know it is not is priced to parents but it was a surprise to the doctors to say that 100% of them have very complex middle and inner ears. Spoke in considering surgery be careful. Not all children with CHARGE syndrome are eligible for cochlear implants if the auditory nerve is not there, that is the nerve that goes from the cochlear to the brain, stimulating the cochlea is not going to help because that nerve that take the message to the brain is not there.

>> Those children may be candidates for brainstem implants where implants directly stimulate the brain and the auditory section of the brainstem to give children some at least some auditory input.

>> But again getting a lot of information before surgery to know whether children are candidates have difficult things might be or what kinds of complications there may be and that is very important before doing any surgery.

>> They look at outcomes for children and there is a variety of outcomes with cochlear implants in children. They found it was very difficult to predict who would have a good outcome. They were not able to say if you have this type of colloquia or this type of auditory nerve or this type of problem there was not a correlation and they were not able to use anything as a predictor of various outcomes. Some children were able to develop speech. Some children simply had sound awareness and some did not appear to have any benefit at all. The vast majority of children do appear to have some benefit from input and some auditory input from cochlear implants but it is not universal. So it is really important to have realistic expectations that it you are expecting speech and miracles and you may end up being very disappointed with the Tran 11.

>> -- Cochlear implants. And another [Indiscernible - muffled audio] consider cochlear implants the younger the better. Younger children are more likely to have better outcomes. It does not mean not consider and older children and they did have some older children that were implanted and they still had some improvements.

>> Another human series was looking at CHD7 findings and that is the Jean that is mutation from CHD7 are found in the mass that is vast majority of children with CHARGE syndrome. So one study looked at where does this Jean come from and the majority of the time it is what is called the two Noble mutation and that means it is new. That the child is the first one in the family with it. However that mutation happened either on the chromosome that came from the mother or the chromosome the came from the father so when they talk about the parental origin of the mutation, they have to be able to tell the difference between chromosome that came from the mother and the chromosome they came from the father and in this study from Germany and were 13 children in which they were able to distinguish the chromosome from the mother and the chromosome from the father and in 12 of those 13 the mutation occurred in chromosome 8 that came from the father and one it did come from the mother.

>> And this is not unique to CHARGE syndrome . This happens because firm turnover the DNA is copied and copied and copied and copied. And the chance of there being a typo in the copying is much higher with when you are copying that many times.

>> The chances you're getting a typo goes up with the more copies. So you see older fathers or advanced paternal age on average with children CHARGE syndrome This does not apply to any particular family budget says as a whole at is how things happen.

>> A second paper that I look that looked at familiar variability and in these families the CHD7 mutation was inherited from one of the parents when they did blood DNA testing on the parents. One of the parents carry the same mutation in the child.

>> The first family they looked at had one child who had absolutely classic clinical charge syndrome -- CHARGE syndrome and they tested that child sibling and that child sibling also had the same mutation. But the only problem that child had was a coloboma and no other features of CHARGE. When they tested the parents the mother carried the CHD7 mutation and she also had a coloboma and she had a very mild distributor problem.

>> A second family they looked at had two children with classic CHARGE syndrome . When they tested the parents the father carried the same mutation in the 2 affected children and his only finding was an unusual here.

>> -- Here.

>> This tells you that there is extreme variation and CHARGE syndrome does not run true in families and it is often recommended to look for the child CHD7 mutation in the parent and that gives you better information and more accurate information about recurrence risk .

>> And once a The CHARGE Syndrome Foundation mutation -- CHD7 mutation has been identified it is simple and not expensive to test other family members for that same mutation.

>> A little bit more on CHD7. I mentioned that Coleman syndrome has overlapped with CHARGE syndrome so what this French group did is they had 209 patients who had Coleman syndrome and did not have CHARGE syndrome or other features besides the pituitary abnormalities and lack of sense of smell that you get in comments and him and out of those 209, 11% had CHD7 mutations .

>> Now that is really interesting because that tells you that one possible outcome of the CHD7 it Tatian is just Kallmann syndrome syndrome and not the entire CHARGE syndrome. The types of mutations they found are what they call Ms. Sands mutations in these are mutations which change one amino acid from another to another one and the CHD7 protein is still produced that simply different. missense.

>> That probably causes your problems than what are called nonsense mutations or truncating mutations which make it so the protein is not produced in all text so the type of mutation you have changes the range of features that you get with clinically.

>> And another study out of the University of Michigan looked at and did a chart review and found patients with semicircular canal abnormalities and identified 12 patients and they did CHD7 testing on all 12 and half of them had CHD7 mutations and when they went back and looked very closely at those

six , five of them actually had CHARGE syndrome. I do not remember if that CHARGE syndrome had previously been recognized but it may not is been.

>> Semicircular canal abnormalities are very common in CHARGE and can be found in people that do not have CHARGE .

>> This is an interesting paper that I came across from a group in France and [Indiscernible - static]

>> Retrospective study that was done meaning meaning that they looked at -- not sure if you can hear that. I'm getting a call in that I am a going pick

>> The study looked at [Indiscernible - static] 60 cases and 40 of them turned out to have CHD7 abnormalities.

>> These were all cases that had been either miscarried or pregnancies that it didn't electively terminated because of significant ultrasound findings.

>> And what kind of prenatal testing is available and what kind of determination is available in France was very different than in the US and probably Canada.

>> The terminations occurred anywhere between 14 weeks and close to term so some of these were fairly far along.

>> But what this study did [Indiscernible - muffled audio] determination had already happened and they went back and looked at and they were able to do autopsies and do information and examine all of these fetuses and do CHD7 testing. Identified what he cases that had CHD7 and they said what kinds of findings did they have?

>> One thing that was really interesting is that of these 40 cases, 29 where male and 11 were female and they were speculating that CHARGE syndrome may be more severe in males than females.

>> Some other groups looking at things have shown preponderance of females later in life which could be because more males do not survive.

>> I do not think we have enough information to confirm that but that is a possibility. They are clearly looking at these of your end of the spectrum but if you look at the table on this slide there are some very interesting findings

>> One is that every single one of them had external ear abnormalities.

>> But half of them had [Indiscernible - muffled audio] Letitia and close to half of them had cleft lip and the vast majority had some circular canal abnormalities in most had heart defects and a line is simply a and brain abnormality and having to do with the sense of smell.

>> 15% of them had I Persepolis which is seen in CHARGE but not at that frequency and in children that survived .

>> And about one third of them had hydro-him family is and this was very interesting.

>> When they look that or another thing that is interesting is that growth was normal and that is consistent with our findings and birth weight is normal with Tilden with and for and the growth falling down comes after birth

>> You do not get growth delay prenatally.

>> When they look at the CHD7 mutations that they found we talked earlier about missense notations and comments and then and only 40 was the missense mutation and all of the others were ones that completely were just -- disable the protein nonsense and [Indiscernible - muffled audio] and one total deletion. So those are what are called truncating mutations. A destroyed the protein itself

>> At the mild end of the spectrum with Ms. Sands mutation you can have something as mild as Kallmann syndrome are some of the parents in the familiar cases with the truncating vacation -- mutation you are shifted towards the [Indiscernible - muffled audio] as far as the medical findings.

>> And the same of the same group had another paper published of a very specific case where based on ultrasound findings and eventually a feeble MRI -- fetal Amorite which showed absence of the semicircular canals they did CHD7 testing during the pregnancy and were able to confirm all the pregnancy was ongoing that it was CHARGE syndrome.

>> Those are some of these case studies in series that I came across. Another thing that happens is review articles and review articles are usually where someone will go and do a literature review and in this particular area and summarize all that literature and there are lots of those available. I will not talk about those in great detail.

>> I was pleased to come across one that talked about diagnosis and management of charge syndrome in the neonatal intensive care unit and this was written by a nurse for a nurse and I think it was published in the nursing Journal and I think that is really helpful to have that kind of information readily available to the people that are caring for these babies with CHARGE syndrome .

>> To plug our own thing a little bit in the Jean review available through the NRH and that is done for physicians and some geneticists on a number of syndromes and the GENE review on CHARGE syndrome does talk about diagnosis and management issue for physicians a well -- as well and there is a lot available.

>> Moving more towards actual studies I want to say okay we have a question we're going to try to answer it for CHARGE syndrome and a very important one was published on death after the neonatal period and this look hairy specifically at seven cases ranging in age from 11 month-22 years and of those seven cases they believe that the death occurred because of respiratory aspiration in five of them. Postoperative complication in one of them. And one choked during eating.

>> And this agrees with what we know anecdotally from Facebook, families that we know that these are the kinds of complications that we see after the newborn period.

>> What they said from this is swallowing problems, gastroesophageal access [Indiscernible - muffled audio] and postoperative airway evidence due to cranial nerve dysfunction are important contributors to post neonatal death in CHARGE syndrome meaning once you get out of the baby period what is been fixed and what can be fixed is fixed. What sort of issues still are there.

>> And one of the conclusions drawn from this is that multidisciplinary feeding teams and treatment of swallowing and reflects issues are absolutely critical in management of children with CHARGE syndrome .

>> Something I tell families is that people with CHARGE syndrome remain medically fragile throughout their lives. Even with ideal management we will continue to lose children with these complications. It is heartbreaking but it is really important to know that a child dying does not necessarily mean that anybody did anything wrong. We do the best we can and even with the best of care we lose some people with CHARGE and that is the toughest part of being involved with CHARGE for so long is that the people that we use.

>> -- Lose. Another study that we look that looked at balance and they looked specifically at 21 children with CHARGE syndrome .

>> 31 control children and these ranged in age from 6-12 years of age and they did questionnaires.

>> They found that more than half of children with CHARGE syndrome are at medium-high risk of falling down. And they had low balance confidence Rick another words they were beery tentative about things. There conclusions were that increased physical activity with focus on balance and movement will likely improve both balance and balance confidence in children.

>> The more you have experience with it, the better you get at it. This includes all kinds of therapies like hypnotherapy and that kind of thing.

>> So seems to hold kids up to hold that the balance helps the confidence also.

>> Sleep apnea. What happens with that? Again this is the questionnaire completed by 51 parents. This was a collaborative study with US and Canada and the Netherlands and was children age 0-14 years.

>> In this study people were recruited and so there is probably a significant ascertainment bias in the 51 children in the study, two thirds of them had been at some point diagnosed with obstructive sleep apnea and that does not mean that expected sleep apnea happens in two thirds. Families that had sleep apnea had sleep apnea problems were more likely to participate in the study. It is frequent in CHARGE . It is not two thirds. So do not worry about your kids that much.

>> The treatments that were reported for these kids included the continuous positive airway pressure. Some had tonsillectomy and or adenoidectomy. Some had eight tracheostomy. All of those treatments helped and there was always improvement after treatment but even after treatment there were often still some residual syndrome -- sometimes.

>> -- Symptoms so the bottom line of this is sleep apnea and obstructive sleep apnea is very common in -- children should be evaluated for it if there is any suspicion and if treatment is helpful but is not likely to completely cure completely eliminate the problem.

>> Another test -- study from France look that cycle motor testing in eight children age 7 years-13 years. And they found some significant patterns in these kids. In the paper they presented the witnesses first and then the strengths -- weaknesses first and then the strengths but I think that is backward so I will do it the other way around.

>> And strengths -- and this was a battery of IQ test and similar sorts of things.

>> There was the strength holistic perception. Semantic competencies. Analogical reasoning and planning skills.

>> The weaknesses included postural control both static and dynamic so difficulty maintaining posture both when sitting and when moving around. Visual spatial constructive abilities. And problems with sequential processing and selective attention.

>> In doing standard IQ tests the range they came out was 54-92 and I think we are all quite aware that standard IQ tests are not particularly helpful or valid in children with century deficit so I would take that with the big grain of salt.

>> Interesting thing that they noted was the extent of the deficits the weaknesses in particular was not associated with the severity of their sensory deficits. So the children with more severe vision and or hearing loss were not necessarily the ones that have the biggest weaknesses.

>> I think what you can draw from that the conclusion you can draw is that specific areas of the brain may well be affected in CHARGE syndrome. So some of the strengths and weaknesses may have to do with how the brain is put together in kids with CHARGE There is a lot more research out there. I am not -- stopping at this level at this point. There is a lot out there and I did not even touch behavior. I think that is a whole separate subject that is covered by other webinars and certainly covered a lot at conference but there's a lot out there.

>> Information is constantly being published on both the medical and behavioral aspects of CHARGE syndrome. Something that is as important for you to know and for you to take back to people working with your kids is the professionals and I mean medical, therapy and educational professionals who are involved with your children have an obligation to find out what is known and to use that information.

>> There is a lot of really good information out there and they need to find it and use it. A lot of the information the useful information is on the CHARGE syndrome foundation website or a link to it there for specially therapeutic and educational information. State deaf blind projects have a lot of information available. Make them go out and look for things for your kids.

>> Moving some people to animals, animal models. What kind of animal models are used? Fruit fly which is also called softly. Zebrafish and mouth and others and is up tables about frogs and chicken

embryos and llamas yes llamas can have coined will atresia and they can have CHD7 equivalent and use can be used for some molecular studies

>> So fruit flies and zebrafish and mice are so of classic animal models that are been used for decades. Although very well studied so changes can easily be investigated. We know a lot about them already so if there is something different it is very easy to pinpoint.

>> Every logically there are more similarities than differences between all of these and people. So they are very helpful. Fruit flies produce very quickly and zebrafish have the particular advantage of the embryos being transparent so you can literally see what is going on while they are still alive and that can be very helpful.

>> And of course are mammals and closer to humans in many of their structures and these ologies so these are all one that are helpful in terms of looking at genetic conditions.

>> And it is important to know that the CHARGE syndrome foundation has been supporting this research. The CHARGE syndrome foundation is a little over 20 years old at this point and we have always supported research. In the early years we were only able to afford to support West generic type of research. $2000 here and there but thanks to a huge increase in fundraising and thank you and thank you especially to our current president David Wells who has done major leaps and bounds in fundraising.

>> We have had a lot more money available and several years ago we surveyed the membership and said what are your priorities and spend the money? And basic science research was one of those top priorities so we have been doing that.

>> In each of the last 3 years the foundation has been able to provide $100,000 per year towards CHARGE syndrome basic science research. That is really exciting and we are really hoping to be able to move even to the next level of that in the near future.

>> And when we give money to researchers, one of the things they have to do is they have to present their work at conferences.

>> This is very exciting and we often hear about cutting edge research and often presenting work in progress that has not been published yet and we are the first ones to hear it.

>> And professional day a conference is one of the places they present that information.

>> Professional day happens on the Thursday before the main international conference which starts on Friday. There is a secret -- separate registration for that. And the families are welcome -- welcome to register and come but at that particular conference, this is set up for researchers to be able to present to each other and talk to each other. I can sometimes barely follow some of these talks.

>> Many of them also present the same information in a more family-friendly way at the fall conference but if you are interested in this you can also -- handouts for professional day are available at the

CHARGE Syndrome Foundation website and some of their power points are available and many of them are not because they did not release the PowerPoint so they are not yet published information.

>> Okay CHD7 is a hot topic and we are very fortunate in the gene that causes CHARGE has turned out to be an interesting and important gene and has therefore gotten a lot of attention.

>> This is a paper published three years ago from the group at the University of Michigan and sort of why CHD7 is so interesting .

>> Well a central question in developmental biology is how proteins like CHD7 and CHD stands for chrome of the main something -- how proteins like CHD7 regulate developmental processes whether they directly activate or repress other genes or act more globally, how does it work?

>> CHD7 is expressed in a wide variety of tissues during development suggesting that it has tissue specific and developmental stage specific roles work

>> So we know from animal studies that the promo domain protein CHD7 is one of that 10 recognize so far. That are very important in a real logic development.

>> Just to remind you hopefully you know a little bit about this, CHD7 -- I do not know where my -- there it is. Chromosome 8 and where the yellow arrow is is where the gene is located. This is the schematic of the CHD7 gene and the dots show where various mutations have been found but that is not -- not the point of this particular -- my showing it to you now.

>> This is what the final protein looks like. This gene here, you see these vertical bars and these are the Exxon's. These are the parts of the gene that will actually code for the protein and all this stuff between the Exxon that is the in turn and the stuff that will be spliced out and not be part of the final protein.

>> These things down here show some of the different important parts of the final protein and act at different places.

>> Now each of these there are 38 Exxon's that have to get spliced together and there is all these interns in there and if you took this entire DNA stretch and wrote it out with the codes of DNA the ATG see and wrote this all out, sketched out although the Z would have a small brook. -- Book it is a huge gene and trying to get it down to the simple stuff is really really difficult.

>> So very big gene so how do you get from the Jean to the protein?

>> Here is sort of a weeks worth of biology class in a single slide.

>> That simplifies first about the DNA is up here and the DNA is unwound and RNA transcript and that is kind scribe from the DNA so you take the template and you transcribed RNA and you still have all of those interns in there and so you have to splice them out. So this is where the interns are spliced out and the poly a tale is added and that then is your messenger RNA or mRNA. The mRNA leaves the nucleus of the cell and then the ribosomes that are in the cytoplasm of the cell attach and we have the ribosomes where that coding gets translated into the amino acids.

>> So every 3 residues from this that has been transcribed from RNA -- DNA to RNA is now translated to a string of amino acids. So the string of amino acids comes on and that is the beginning of the protein.

>> Even that is not the whole thing. So once that protein has been be a mineral acids are strung out, this is sort of the little cartoon showing it again. So you have the DNA. That is transcribed to RNA and then the in neutrons are spliced out and then you have the messenger RNA which at the ribosomes is then translated to the string of amino acids -- sorry I'm using my pointer which you are not seen. The string of amino acids here and then there is what is called post-translational modification where you get that final protein.

>> So there are many many steps going on there and things can go wrong at every step in there can be interactions at every step.

>> Now a little bit of how we or how this all happened and so what we looking at? Well if you're using an animal model first you have to figure out that the animal had something equivalent to CHARGE syndrome .

>> Some animals have been very well studied and the gene figured out and already named and you need to figure out given one of those gene that human equivalent of the CHD7 gene. In the fruit fly there was already a gene maintenant was called Tesla and I really love this -- coloboma. -- Kismet. Kismet is not random it is Hindu for fate or fortune.

>> Years ago the Drosophila researcher who was identifying many genes and naming then was really into Hindu philosophy and he recognized that this particular gene was crucial in the overall development and the overall fate of the flies and so he named it Kismet So the fruit fly equivalent of CHD7 is Kismet . So this was a cover story on human molecular genetics just about exactly 4 years ago.

>> What is this a picture of? Which you have over here are normal fertilized and this is for July with Kismet and this is normal and this is with Kismet. Haitians with charge have hypocapnia and flies with Kismet have hypocapnia and they cannot keep their wings like this and their wings dropdown and their legs -- they have hypertonia just like the kids.

>> Kismet flies have defective immediate recall memory. Kismet have defective motor reflex function so okay they have some hypertonia and motor problems. If this muscle and this nerve -- well when you are using flies, you can take them apart. Figure out what is going on there you cannot do that with people so what they did is they looked at this and they found their actually is an abnormality in the muscle cells of the flies and it is a reasonable thing to assume that they are probably abnormalities in the muscles themselves in children with CHARGE syndrome There are many functional equivalence to what you see in children with CHARGE syndrome .

>> Moving from pies -- flies to zebrafish embryos and you can see them at the different stages. The CHD7 protein has been stained blue so you can see where it is active. And what kind of effect does CHD7 have in zebrafish? Well they have absent retinal nerve cells. A have abnormal organization of their cranial motor neurons. They have defective otoliths and that is there inner ear and in fact what

happens with the embryos with CHD7 is they lie on their side and they swim in circles because of the abnormal inner ears perk

>> They have a loss of facial nerves and irregular vertebrate and reduced bone mineralization so again you can see many features that are very similar to what is seen in children with CHARGE and since you have those same features then you can try to manipulate the embryos and see if you can make any of them better.

>> You can also look and see where do these effects come from.

>> Several labs have looked at zebrafish and so CHD7 as acting at at least two levels. Remember DNA is transcribed into RNA and then RNA is translated into protein. CHD7 at that oath of those levels to other genes so it goes in and causes other genes to be transcribed or stop them from being transcribed so it turns them on or off.

>> It also changes how fast and how they are translated into protein.

>> So CHD7 is affecting a lot of other genes. That is part of how you can have a single gene that can wreak havoc in many many different organ systems.

>> They actually in manipulating the zebrafish they were able -- two different labs found two different ways to actually event some of these effects.

>> This one is complicated and in the -- I barely understand exactly what they did so in the interest of time, I am going to not describe in detail but this is wild type and completely normal and this is control also completely normal. These are at variance of CHD7 embryos and you can see they are very abnormal in their shape if nothing else. And this is a CHD7 embryo that has been rescued . So they found a way to inject something that prevented the effects of CHD7 .

>> That may eventually lead to something that might be helpful in people.

>> Another lab looking at it from a different point of view said okay CHD7 is required for Robert organization of neural crest -- neural crest derived cranial facial cartridge -- Cartledge structures but in CHD7 knockout there is elevated expression of cell cycle inhibitors resulting in reduced cell filtration -- proliferation.

>> When they said okay can we reverse this reduced cell proliferation so they found another Jean that -- gene that goes the other direction and they found so additionally knocking out a normal repressor gene rescued for cell proliferation and Arledge defects so this led to a complete rescue of CHARGE syndrome phenotype in zebrafish so they were able to cure it.

>> So this is something that may actually lead to something we can look at for people as well.

>> So that was a very exciting presentation.

>> Moving onto first my smiles was developed within the first year CHD7 being identified as the can for gene and this is looking at charge embryos and you can see that again the CHD7 protein is stained blue and is in the heart and in the tour Terry and the back of the brain and in the ear and in the eyes and the retina. So it is active in same place it is in people.

>> They had to do some manipulation to see some of the features. If a mouse is missing one copy of a CHD7 gene they do not get the cranial facial features that you see in people. You still get normal I and normal cranial facial structures but there is a way -- if you knockout both copies of CHD7 in a mouse it is legal. But what they can do is called a conditional knockout where they are able to do a double knockout of the transport and eight Justin serpent -- CHARGE gene certain tissues and that is where you get a short nosed and the I findings -- eye findings.

>> So they confirmed in mice that CHD7 has similar effects in people and affecting some of the same structures.

>> Other my findings were CHD7 is necessary for development of the cerebral cortex and regulates neural stem cells and inner your development and causes distinctive abnormalities very similar to in humans.

>> And this is really an exciting paper that was published last year now CHD7 contributes to your Genesis that is formation of new nerve cells in the part of the brain called the Hippocampal and it does this throughout life in mice and people and adults mice with CHD7 the euro Campo neurogenesis is decreased. Hippocampal neurogenesis is also affected by exercise so these researchers took CHD7 deficient mice and put them in exercise wheels I did not force them but left them alone on the wheel and there neurogenesis improving got a little better in that one way.

>> What they found is that exercise induced neurogenesis seems to bypass CHD7 . The CHD7 halfway in mice.

>> These data suggest that exercise-induced neurogenesis is probably CHD7 independent indicating an alternative pathway that can drive neuronal differentiation in the absence of CHD7 .

>> At least in the Hippocampal area and this is the illustration where showing that charge syndrome -- turn for syndrome reduces the neurogenesis but you can bypass that with exercise and I think this is the another thing saying exercise might actually be a really good thing for people with CHARGE .

>> I am going to try and speedup a little bit because I know we are short on time and I would like to try to get Salemme -- some questions of a cannon this is a very long story short. CHD7 which is in the center here and these are some of the other genes that are known to interact with CHD7 and it interacts with hundreds of other genes.

>> Because it interacts with so many other genes, it is likely there are other ways to get to clinical charge syndrome.

>> ~With all the features of CHARGE syndrome but no mutation . And I actually see a question asking is CHD7 and epigenetic gene? Epigenetic is the interaction of genes and absolutely the CHD7 genes are all epigenetic. Hardware to say

>> Most genes probably are and only beginning to understand interactions about these things and that is part of why and seven was so interesting to all of the researchers.

>> If it is interacting with all of those other genes and you have all these other ways [Indiscernible - muffled audio] interacting with maybe with those interactions you can get kids that have clinical CHARGE syndrome that do not have a CHD7 mutation.

>> How can this happen? Upstream there may be gins in itself that interfere with CHD7 function and then you get all of the downstream -- problems from their.

>> Or downstream there may be critical genes that CHD7 affects that might themselves be abnormal and come up with some of the same effects.

>> That is some of the ways you can get to a CHARGE syndrome finical picture without a CHD7 need Tatian.

>> A plot -- mutation.

>> Up I that two people so one of the things they did in mice was look at the whole genome of the mouse and fine look at CHD7 mice and normal wild type mice and see what different things are expressed differently in those 2 different mice.

>> They found and identified 98 genes that were expressed differently in CHD7 in wild type and so they look at some of those 98 genes and they picked one out and it is SEMA3A. Then they said I wonder if that could be another pathway to get to CHARGE syndrome.

>> So they looked at 45 patients with CHARGE syndrome . Clinical charge syndrome who did not have identified all the -- identifiable mutations and in the had a 45 day count this is from the mutations they were looking at and this was reported very recently but this is a clear thing saying yes there are other genes that can interact with some of the same pathways of getting some of the same features.

>> They likely will have a lot of the same kind of complications as kids with CHARGE Another one is a protein called P 53. CHD7 the CHD7 gene product binds to P 53 promoter and reduces its activity.

>> If you just increase activity so if you lose a normal CHD7 that means he will have increased -- so if you have -- lose CHD7 and you have a mutation then you will increase P 53.

>> If you do not have CHD7 but you simply increase P 53 activity then you can get the features of CHARGE without a CHARGE mutation .

>> Wonder what that might be? Maybe if you suppress P 53 activity you might reduce the features of CHARGE so look at negative regulators of their P did the three a possible therapeutic targets for people.

>> So that is something that is in the -- it is a really cool idea stage and in fact the CHARGE Syndrome Foundation is funding one of the researchers that is looking at this question.

>> I will quickly go through putting this all together and then I will try to get to some of your question so I think we will have time for some of that.

>> Because there was a lovely paper put together that sort of puts a lot of this together, knowledge from people, I sent molecular work and this was a collaborative effort between the group in the Netherlands Connie Ben Raven weight and Nicole question Johnson and some of the people that I've been working on CHARGE for longtime and they found the gene and they collaborated with individuals that chop which is the Children's Hospital of Philadelphia one of the world expert on 20 2Q deletions and I think as most of you know 22 20 2Q deletion is a very closely related to CHARGE and terms of the overlap between the syndromes .

>> So they look at and compare the relative frequency of the features and they look that which Jean caused the features in some confusing cases and they had hypothesized some about mechanisms.

>> This is a table from their paper which is just lovely. What it looks that is it says okay here are all the features. Here is how common they are in 22q deletion syndrome and here is how common they are in CHD7 mutation and the frequencies for each and these were huge numbers.

>> The CHD7 group they were looking at had up to 800 cases. Note the look over here and they only knew about cranial nerve dysfunction in 174 those cases but really for all of these they had a lot of information.

>> The folks at chop had information on it table of about 1300 people and 22q deletion and they listed these as the ones most common and CHARGE and the ones most common in 22q so you can see the lack of sense of smell and it is common in CHARGE but it is unknown in 22q.

>> Semicircular canal activities very rare in CHARGE and where it seems in 22q so that is an important thing to note for later.

>> And if you go down to the hypocapnia that something is generally not reported in the database that they had for CHD7. We know what happens and there are kids with CHARGE that have an absent farm is and low calcium but it is much less common as seen in two thirds of kids with 22q and any small percentage and [Indiscernible - muffled audio] motor delay and ear abnormalities in the two conditions are different but they are very common in both.

>> Heart defects common in both. Heart defects are exactly the same and -- in both of those.

>> So that is the first thing that they show their. -8 there. that was really really interesting.

>> If you look at how common these things are okay CHARGE syndrome happens they figure about one in every 15,000 births. 22q Deletion is somewhat common probably more like one in 5000 and if you look very closely kids with 22q the Jean that is actually -- actually causing the features is PBS one and

some of had TBX one testing and some of had 22q testing and they look very specifically at TBX want to get some good information out of that so they had one -- 802 kids that were positive for CHD7 and they looked and said how many of those typically have 22q features and they found typical 22q features and 30 of those so let's make sure none of those have a double that noses they did not have to be excellent mutations. Next they look that a diagnosis of CHARGE but do not have a CHD7 mutation and did not know how many of those were but they did find 5 that had 22q deletion so it looked like they had CHARGE but the cause of it was really 22q.

>> The other way around they look the kids that they had or thought they had 22q but the TBX one 22q was negative and of those [Indiscernible - muffled audio]

>> So again there is tremendous overlap between those and you can really look like you have CHARGE and maybe have 22q an to be is one and the other way around.

>> So why are these overlapping?

>> Well likely they function in the same embryonic pathways and the hit Carmen target for both the panel that's just common target for developmental genes and from animal studies and observations both TBX 1 and CHD7 regulate gene transcription and may well regulate transcription of the same downstream gene so there are probably affecting some of the same pathways.

>> This is just a schematic showing some of the TBX one and CHD7 and then this is just showing some of the genes involved in neural development and the pathways common that they can affect each other.

>> Many of the other genes that are downstream genes for both to be excellent and CHD7 cause other syndromes that have features that overlap with them.

>> So it is likely that there are -- they are over at -- interacting and very complicate it ways that we only begin to understand okay so how do they tie this people study in with mice? They went and looked at my thing created mice that had both CHD7 and TBX one so what do they look like ?

>> Not surprisingly they had very severe heart defects and most of them died in the newborn period but also very interesting is they also had abnormal thymus which is very [Indiscernible - muffled audio] and they all had semicircular canal abnormalities so they really did have both. They had severe things that you seem in both and they had features of both syndromes.

>> And again it is suggesting that the genes are acting in the same developmental pathway.

>> Again this is research supported by the CHARGE Syndrome Foundation .

>> I will let you look at this when you download the PowerPoint and this is just showing a bunch of genes and this is all of the CHARGE features and how often these CHARGE feature show up in some of these other conditions .

>> I was a little surprised they did not include kabuki syndrome in here because it has a bigger overlap as many of the syndromes.

>> Getting quickly to what is going on, the foundation has provided grants in 2012 and 2013 looking at cranial facial development, DNA, regulation, heart and college uncle defects and sensory deficits and brain patterning and really finding some exciting research and in CHARGE anagrams we're getting out this year , one is to look at MRIs taken of people with CHARGE to see if there are any specific patterns for the brain abnormalities. Another is looking at the role of CHD7 in nerve function. And seven and gene regulation and the P 53 study as therapeutic targets as I mentioned. Those are what is coming from all of that fundraising you guys are doing it is going to really exciting stuff.

>> The last slide in my presentation is a plug for my database project. Which is supported by the CHARGE Syndrome Foundation if you go to the webpage it is the blue button on the right side and we would like to have bigger numbers for clinical findings and it also can be used as a registry so if there is a research study that we like people to participate in then I can find you and contact you and say would you like to participate?

>> We need you for that.

>> That is the end of my formal presentation. I have a little bit of time for questions and I do not know if I should just go through some of these questions on the side here? Does that work for people?

>> Let me say tech

>> You can either go through them yourself, made. Or I can try to read them for you.

>> And this is Lori.

>> Yes I got to Lori. One question was that I understand correctly CHD7 deletions and other truncating mutations indicate more severe CHARGE to make their correlated with more severe CHARGE there is not more than one . You cannot say if it is a truncating it will be severe. If it is missense then it will not be. When you look at large groups that is the trend. Unfortunately you just cannot predict that for anyone individual and if you look at the families, people in the family have the same mutations and some people have much more severe medical features than others.

>> So as a whole and a large group, there is that trends. It is not useful for individuals. And it is an epigenetic gene to make yes it is and that is a whole other webinar in itself.

>> And the hippocampus and exercised up and come I do not understand the medicine well enough to be able to answer the question about that that is something that maybe we can get somebody to talk about at the next conference. If that is something that might actually be therapeutic and helpful for people that might be a good topic for conference.

>> If you are going to do a charge rescue must it be done in utero? Well to get a complete rescue, yes and obviously that is not something that is likely to be helpful in people.

>> But there may be things -- it is clear that CHD7 is having its effect throughout life. And if there are things that we can do to make life easier, or help some of the things get better over time in people with CHARGE then that would be useful to know . Especially if there is a change in brain that can help.

>> Yes whether we will be able to rescue or cure, probably not. But who knows what that will lead to in the future.

>> Golden heart syndrome, how does that compare when sitting with CHARGE? It has a lot -- it does have a lot of overlap and a lot of the same features. Olden heart does not generally have a gene associated with it. It is more a collection of things and so testing for all of the known genes that have overlap with those features as they did with your child.

>> How likely would it be to have a person 22 20 2Q in charge? Well if you look at the frequency one in 5001 and 15,000 and if you multiply those together then who is good at math?

>> I had thought with the Dutch group had a patient with both but they are the ones who did this latest report and they said they have not yet identified one. They know the most people with both of those so I do not yet know of a person that has both of those mutations.

>> Based on the mouse study I would expect it would probably be legal because they had such severe heart defects and the mice died and so a CHARGE plus 22q might not make it through pregnancy.

>> Lori, that I miss questions?

>> Yes you missed one by Melody. She asked is the auditory brainstem implant safe for children and or adults with CHARGE ?

>> It has been done in at least a couple of kids with CHARGE . Like any brain surgery you would want to have very very careful evaluation and counseling to know what that potential complication and risk are associated with that.

>> But it is something that has been successfully done at least in a couple of children with CHARGE that I am aware of . So it is certainly worth investigating.

>> You can pick up by Chris Russell has a lengthy question.

>> Okay you mentioned a study that found patterns of asymmetry between the eyes. Doesn't mean that children with CHARGE are at high risk for an isometric be a? I do not know what that is. That might

>> -- [Laughter] can anybody help me with that?

>> Maybe you could go on to the question with Olivia. At the same mutations do not have the same features, what are other mechanisms that can contribute to this?

>> I him not sure what you are asking -- I'm not sure what you're asking Libya -- Olivia. Not sure if you're asking about the same CHD7 mutations or -- we can look at trends with mutations. We cannot look specifically. A lot of people have said is there a -- to mutations in axons 32 cause more severe problems

then you know in a different Exxon are types of mutation? And for the most part those are what are called Sigma type genotype that does the Jean predict what the medical problems are income those really have not held together. They really do not.

>> That is probably because there are so many other genes that are involved. If CHD7 is acting on hundreds of other genes, those hundreds of other genes are all going to be different and all make things better or worse and that kind of thing.

>> That is probably part of why you have parents and children who both have CHARGE or siblings who both have CHARGE who have different features. Unless they are identical twins, there other genes are different and so when you combine them all together you are going to get some different effects.

>> That said even identical twins with CHARGE do not have identical features . Because it is not just genetic. It is you the rope provisioning. Nutrients from the placenta and all kinds of other things that we are only beginning to understand. This is all very complicated and we're scratching the surface in getting more information, but we do not have all the answers for it.

>> So Olivia I hope that answered your question.

>> [Indiscernible - multiple speakers]

>> As in the case of kabuki syndrome the mutation is with genetic gene which is preventing a specific part of the DNA not expressing, does this mean that the optional DNA does not have a mutation?

>> I think what you are asking -- like if you have CHD7 mutations and it is turning on and off other genes, are those other genes normal and in most cases they probably are and the interfering with those other genes is probably part of why if a different person just has a mutation in that other Jean they have some features that may overlap with features in CHARGE syndrome -- CHARGE and that is all supposition and the animal studies are very helpful in looking at that because you can manipulate the animals and give them those other conditions and see what is going on.

>> You can also manipulate the animal who has different backgrounds and see if that changes the severity of things.

>> I know that at least one human researcher was very interested in looking at other genes that may influence the severity of CHARGE syndrome and so there are a lot of interesting stuff that is going to happen in the future work we will probably have to do this kind of a webinar as a regular thing to keep updated on things. We do try to update with brats from the foundation and the conferences and the kinds of thing too.

>> [Indiscernible - multiple speakers]

>> Russell finds the term that you were having difficulty with. Do you see?

>> Difference in prescription between the eyes is that -- very likely there will be difference in prescription between the I. I think most people in my prescription is re-different from the other I and I

would expect that with two eyes being different that the vaginal -- visual acuity is very likely to be different in the two eyes.

>> Yes there is a lot of stuff with that.

>> Then we have the question what are the neurogenesis hippocampus effects that can be improved with exercise?

>> I do not know enough about the medicine involved in that and the functions of the hippocampus to be able to answer that question.

>> I remember that yes Rick

>> But what is going on in that is in most parts of body their cells are not being regenerated all the time and that is a part of the body where they are and so they are constantly being made and CHD7 is interfering with them be made and so exercise can bypass that and keep them being made at a more normal rate.

>> What that does for your body I cannot answer.

>> Okay

>> Jan and a call after people who have the same deletion mutation in the same places on the sequence CHD7 have the same type of defects or can make genetics present differently in each kid?

>> Yes, yes. Again if you go back to the family study, if someone has inherited a CHD7 mutation from their parents then that parent and that child have the identical CHD7 mutation so they almost always have very different features.

>> It would be really nice if we could say this mutation causes this problem and you know this mutation in exon six causes this problem. Does not work that way with CHARGE. Work obligated with that unfortunately .

>> The CHD7 usually associated with neural crest distribution? The study mentioned on the P 53 suppression, what that treatment potentially help afterbirth or only prenatally?

>> I think that has yet -- it would be very difficult to find something that would be helpful prenatally so much of the problems with CHARGE happened very early in early embryos in the first couple of months of pregnancy and if they're able to treat something there without causing all kinds of problems, is far in the future if at all.

>> But there may be -- children with a diagnosis of CHARGE there may be something that you can improve on by postnatal development. Exactly what those would be? I do not know yet. Stay tuned.

>> Bonnie asked my son was diagnosed originally with golden heart syndrome yet fits with the CHARGE yet actually had [Indiscernible - muffled audio] since been diagnosed with trisomy nine get all of that action would trisomy nine children looks like children with CHARGE.

>> There are hundreds of syndromes that have features that overlap with CHARGE and when you say look like it really depends on your perspective. If you list the medical features [Indiscernible - muffled audio] huge on that. When you look at some of the more gestalt things the particular shape of the year and the particular shape of the ears and hands in that kind of thing, it is typically -- that is sometimes or you -- the geneticist might be able to distinguish features of some of the syndromes from each other. I mean the little girl I followed so long who has kabuki absolutely no question it is CHARGE syndrome on paper but we always look at her and say you know she just does not look like it and that conference families will say yes your children has CHARGE but was a little different than my child so there are some subtle things that are different in the kids . Doesn't matter? Well for a lot of the medical problems of the charge of the information from CHARGE gives you good information for your kids and that is wonderful.

>> As far as recurrence risk and possible things coming up in the future those things may be different with different syndromes so you have to be a little careful not to over generalize from the syndromes but certainly there's a lot of overlapping and useful information that goes on in both

>> [Indiscernible - multiple speakers]

>> For an individual diagnosed with CHARGE ? Yes I'll answer that very quickly. Think it is helpful for the family to know and to get information for people and if you can get your insurance to pay for it then yes

>> Wonderful. Made -- Meg, thank you so much.

>> Okay. You are welcome and I think that will cut us off from this if you have other questions send notes to the foundation and to me and give us topics for future webinars and for presentations at conference.

>> Meg, Thank you so much for an impressive webinar and we appreciate the time and effort you put into this presentation. Was very informative.

>> You are welcome and I hope it is useful and I hope we can do this again to get more updates because everything is moving really quickly which is exciting.

>> Good night everybody.

>> [event concluded]