

WOLTERS KLUWER

Moderator: Leon Henderson
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3:00 p.m. CT

Operator: Good afternoon. My name is (Jerrie), and I will be your conference operator today. At this time, I would like to welcome everyone to the Genetics in Medicine conference call. All lines have been placed on mute to prevent any background noise. After the speaker's remarks, there will be a question-and-answer session.

If you would like to ask a question during this time, simply press star then the number one on your telephone keypad. If you would like to withdraw your question, press the pound key.

Thank you. I would now like to turn the call over to (Dr. Henderson), so that we may begin.

Leon Henderson: Thank you very much (Jerrie), and welcome everyone. My name is (Dr. Leon Henderson), and I'm an analyst for the inThought Expert Discussion Series. Welcome to the Expert Discussion Series. Today's topic is Genetics in Medicine, and we are very fortunate to have with us today, Dr. (Edward McCabe), the Physician in Chief of the Mattel Children's Hospital at UCLA, and the Mattel Executive Endowed Chair in Pediatrics. Welcome, Dr. McCabe.

(Edward McCabe): Thank you.

Leon Henderson: I know it has been a busy year for you being the leader of several opportunities, what is your goal for your research interests throughout your

career, as well as how you spent the past year directing leadership in medical genetics and translating it into clinical practice.

(Edward McCabe): Well, I am very fortunate that Russians launched Sputnik, because I'm a first generation college attendee, and got involved in one of the maths and science enrichment programs at the age of 15 at the University of Maryland School of Medicine. That was in the pediatric research laboratory. I stayed with that laboratory through high school, college at Johns Hopkins University, and then started my MD-PhD at the University of Maryland.

My advisor moved to the University of Southern California. So, I've moved with him, but that – up until I would say the mid-80s, I was more in a biochemist role, and understanding pathogenesis of disease, and then made a shift in the mid – late 80s to molecular genetics, and have been moving from the more traditional molecular genetics, cloning and characterizing genes to now moving into the molecular medicine, genomic medicine, personalized medicine area.

Leon Henderson: Wonderful, and I know that you have been the leader, the president of The American Society of Human Genetics, the Society of Inborn Errors of Metabolism, the International Society, I believe. Tell us about the last year and activities that you feel are of great value that you discovered in your leadership roles?

(Edward McCabe): Well, the year included two presidencies. I was the president of the International Congress on Inborn Errors of Metabolism of the 11th International Congress. That was held in late August, early September in San Diego and really responsible in large part for putting that program together, and identifying the plenary speakers. It was great fun, and I still am a biochemical geneticist, and feel very much part of that community.

But, I was also elected to be president of the American Society of Human Genetics, which is the largest genetics research organization in the world, and that was a lot of fun. That really involved routine; I think every other week, conference calls, often daily calls with the executive vice president, Joann Boughman, to discuss various business activities of the society that

culminated in the annual meeting this fall. I think six weeks after the ICIEM congress. And it was held in Hawaii, which was great fun and a wonderful venue for meeting. And we had attendance that we were just – for both of those meetings, we had attendances that far exceeded our expectations.

Leon Henderson: And I was fortunate enough to be at both meetings, and we saw a lot of activity at both ICIEM and ASHG surrounding – and this I think is some of your expertise in inborn errors of metabolism, but (inaudible) seem to be a large topic, and I know that folks were pretty excited about the advancement of Kuvan. I'm not sure if it has gotten as much activity as clinicians would want, and I'm curious as to your opinion about the agent, and where it might go from here?

(Edward McCabe): Well, being a biochemical geneticist, as PKU is our biggest disease that we deal with, there is a major move afoot, that I don't – I know that I didn't predict. Back in the 80s, I think a lot of us thought that we would be seeing gene therapy, before we even thought about enzyme replacement therapy. I know, I realized that gene therapy wasn't living up to its hype, when I had been telling my patients that it could be five years away for about 10 years.

And I think enzyme replacement therapy, first with Gaucher disease, and then with a series of disorders and the Kuvan for PKU is really an exciting opportunity, and you know, you said it hasn't quite caught on as much as we might expect, and that is a shift that we are always very cautious in medicine, and biochemical genetics is no different.

So, I think some of the leading centers are really excited about it, but they have been doing some of the studies, and I think it remains to be seen how it will change our management, but certainly the trials look quite exciting.

Leon Henderson: And do you think in the real world, it is helping individuals in terms of reducing the burden of the unattractive diet? How has that been going in the real world and do you see a shift towards greater uses as folks gain experience with the agent?

(Edward McCabe): Yes, I think we will see increased use of Kuvan. I was excited. I saw something that came from the parent's organization last week, and something

that I had actually looked into in the late 80s, when I was at the Baylor College of Medicine in Houston. We were just beginning to get search engines for looking at protein sequences, and I thought, wouldn't it be great if we could find a natural protein that was low in phenylalanine, and apparently a company is making that now.

So, it is a natural protein. It is not, you know, one of these (hydrozulates). The PKU diet, for anybody who is not aware, the PKU diet is pretty disgusting. And I feel – I am one of those physicians that feels that if one is prescribing a diet like that, one needs to know what it tastes like, so that you can really explain it to the kid, and I got good enough at tasting it that there was a batch of the diet that came out, and the fats had actually gone rancid, and all the kids naturally were complaining that this is really bad, and everybody else had tasted it as well.

I can't tell the difference between that and a routine diet, and I was actually able to say, 'Yes, this is worse than usual,' and get back to the company and have them look into it, it was a batch of the fats in the diet had gone rancid. So the diet is a real challenge. The diet for PKU is lifelong, and we have got to come up with some better ways. I'm hopeful that this natural protein that is low in phenylalanine that according to the testimonies from the families and the kids tastes a lot better than the regular diet. That could make a huge difference.

Leon Henderson: And right now, this is whereabouts in its development, and is it complimentary to Kuvan or is it something that...

(Edward McCabe): I think it will be complimentary to the Kuvan. They are really acting in different ways.

Leon Henderson: OK, and I understand that we are also going to be – we're also on the verge of the BH4 compound, coming forward in the Phase II, Phase III transition, and how do you envision that being used?

(Edward McCabe): Well, we have used – a lot of us have used tetrahydrobiopterin to do challenges and to identify those kids that respond to the BH4, and some kids will respond to that, not all. But I think that will be a big help for some of

them, and it is interesting because we talk about chaperones, where actually chemicals can change the shape of an enzyme to make it more active. And there are natural chaperones proteins in ourselves, and then there are small molecule chaperones, some of which look like substrates and some may be pseudosubstrates.

It appears that BH4 may have a chaperone activity. So, it is not just those who were not making adequate BH4, but some patients with some of the mutations in the phenylalanine hydroxylase that looks like BH4 may make it more active. So, we are assuming that it is a chaperone-type activity there. I think we're going to be seeing more chaperone therapeutics. There are a couple of companies that actually have this as their primary business plan.

Leon Henderson: And we have been taking a look, not only at BioMarin, which is developing the BH analog, but also by Amicus Therapeutics. It is interesting to note that because the literature was – there was, what I would call a dearth of literature that generated evidence that there was a chaperone function in BH4, and now that seems to be burgeoning, sort of in parallel with the potential chaperones in Gaucher and (inaudible), for instance, that Amicus is developing. Do you see these agents as complimentary agents, as agents one would use serially with the enzyme replacement or the enzyme analogue therapy or...

(Edward McCabe): I think, enzyme replacement is extremely expensive, and I think if there is a way to make the residual enzyme activity higher using chaperones that will probably reduce the amount of enzyme replacement therapy, which will save money in the long run. So, I think they will be used together.

Leon Henderson: And in what other single gene disorders do you feel that this would be appropriate for?

(Edward McCabe): Well, I think it is just going through the inborn errors of metabolism, and looking at where there are opportunities to develop chaperones, where there are opportunities to develop enzyme replacement therapy. The problem with all of these is that these are rare diseases. And so the companies developing them put a lot of money in upfront, and the return in terms of number of

patients that are going to utilize it, they are orphan diseases, and so they end up being extremely expensive.

Emil Kakkis for full disclosure, Dr. Kakkis got his MD PhD at UCLA. He was on the UCLA faculty at Harbor-UCLA, and they hold a patent for the first enzyme replacement therapy for MPS type 1. But Emil founded, or was one of the cofounders of BioMarin. He is a young man, but has made considerable amount of money, has established a foundation to really try and get the attention of the federal government and the FDA that took them – I think they expected to have two years to go to market, and it took them 6 years.

I forget the amount of money, but it was like 6 to 10 fold the amount of money that they had anticipated, and a lot of it was because the folks at the FDA did not understand the differences between a blockbuster antidepressant and an orphan enzyme replacement therapy. So, he is really taking his foundation to try and educate folks that it is not a sustainable model the one we have now for getting these orphan disease therapies to market.

Leon Henderson: And why don't we go with that idea a little bit longer, we saw at ASHG some ideas coming forward regarding the direction that in the future of getting orphan disease to market, but the funny thing is that we are often very impressed and encouraged by what, for instance, BioMarin has done, what some other organizations have done in getting these to market and also becoming successful companies, but perhaps the way over the past is sort of a (inaudible), and we need novel ways to introduce these to the market, and it seems sometimes that the FDA falls behind the pace I guess, of the scientific discoveries and the needs of the society.

So, what should we look for that sort of helps us understand that we are going to be at that next wave, where there will be better incentives for these modalities to go forward.

Leon Henderson: You are sounding much more optimistic than I think I am, because, you know, the FDA is an extremely conservative organization, and I will cite the example for being conservative has been to the benefit of patients, and I

certainly agree with those examples. The problem is their conservatism and the speed of discovery may now be to the point where they are hurting patients by their conservative nature.

And when parents are demanding these drugs and willing, because of – there were examples that were cited at the American Society of Human Genetics meeting, where kids have died and parents were calling out saying, 'Don't let my kid die. We will be happy to enroll in a clinical trial.' You know, if my kid is going to die, I am willing to accept that there is some risk of side effects. So, let us go and let us try and advance knowledge, and the FDA have said, 'No, no, no. We will let your child die, rather than be too quick.'

So, I think that we have to recognize that going too slow may have the same problems of going too fast, and the FDA needs to learn how to be a little more nimble in the modern marketplace.

Leon Henderson: That is interesting that you bring that up. We have had several examples in (Garden-variety) disease, and non-orphan disease lately, where we have seen sometimes the risk averse nature of the FDA certainly, I feel and we feel as an organization and a lot of the progress and some of the management decisions seem to be in the administrative hands as opposed to the clinician hands. Are there movements afoot that you think are going to take hold soon or at least if not soon, in the foreseeable future where we will be ushered into a next wave of – if not non-conservatism at least advancing some of the agents – we had today BioMarin introducing a therapy, a small molecule therapy, duchenne muscular dystrophy in Phase I, for instance.

We have had other organizations Vertex, for instance, advancing cystic fibrosis therapy that appears to address some of the molecular issues at play in cystic fibrosis. These seem to face the prospects of being stalled, unless we otherwise find a remedy for this. What should we look for?

(Edward McCabe): Well, I think we are entering a phase, where we have high throughput for drug discovery. Drug discovery is no longer just a random and hypothesis driven, you can take libraries of tens, hundreds of thousands of molecules, develop high throughput assays and identify drugs that are out there, and there

are quite a few. There are tens of thousands of drugs that are already FDA approved, and that is a library people go to first, because basically you would be using them off-label in the clinical trials for a new disease, I think it is an exciting phase.

But I think we're going to see faster and faster recognition of new molecules that can be used therapeutically. So, I think it is exciting because of the technology. I think it is disappointing because of the bureaucratic burdens that are placed in front of these.

Leon Henderson: Any clinicians aside from Dr. Kakkis making headway into getting the clinicians viewpoint better addressed at the organization?

(Edward McCabe): Well, I think one of the things that – I chaired the Secretary's Advisory Committee on Genetic Testing under Clinton and Bush, and then Secretary's Advisory Committee on Genetics, Health, and Society under George W. Bush. And so I've done advisory work inside the beltway, and right after Dr. Kakkis had a meeting – immediately following the ASHG meeting, I went to the executive secretary of the SACGHS to suggest that they might want to hear his side of the story.

And represented on the secretary's advisory, Secretary of Health and Human Services Advisory Committee is the FDA, as well as many other federal agencies. And so seeing if Dr. Kakkis could get there, and I have offered to emulate if there is anything I can do to help him, I am happy to do it. I think this is a very important activity. I think that Emil knows it. His company almost went bankrupt.

His product almost didn't come to market, and you have talked about other products in the pipeline, but he tells a very compelling story about why it is important that we begin to try and recognize that orphan drugs for orphan diseases need to be treated differently.

Leon Henderson: And we hope the bottleneck is relieved thanks to his and your efforts, and we look for those signals over the coming year as we get a lot more in Phase I and Phase II that we like to move forward. I know, they have (working on) drug and they have some coming down the pipe, thanks to a lot of research that was

initiated here. You talked about gene therapy, and you know, where it is almost like in garden variety medicine being the decade of the brain for the last several decades, where are we now and what should we, you know, sanely and sagely advise people as to its evolving utility or in utility?

(Edward McCabe): I think that there were an awful lot of people that were hyping gene therapy. And the NIH director put together a couple of panels that both concluded more smoke than fire, more hype than hope, and we need to really go back to the bench and start from the beginning, and not make wild claims about gene therapy for cystic fibrosis that really weren't going to have enough impact to do anything.

So, I think that they have done that, there are some lengthy viral clinical trials. I think the adenovirus, you know, our systems are very good at developing an immune response to the adenovirus. We need to look at tools that maybe don't rev up our immune system quite as much. I think many of us had hoped that if you carved enough of those viral coding genes out of the vector, that you would be OK. But that hasn't been the case.

We are very good at responding to the viral codes of many viruses, and you can't have viral gene therapy if you don't have a virus. I think some of us are excited. I know I am, and my lab is, about nanoparticles. Other people are very concerned about nanoparticles, and that nanoparticles will be the – that they will be killing cells, and cells will apoptose, and all of these things that it is just the next go round of the hype of gene therapy.

But I can tell you, we are looking at nanoparticles, and some appear to be safe are in Phase I clinical trials. The NIH, and I'm not sure if it is NIH or NFTA but there is a program at the federal level to really try and get nanoparticles into the marketplace and foster Phase I clinical trials.

So, I think that I'm excited about that. I'm a member of the California NanoSystems Institute here at UCLA, and I think there is a lot of promise. One of the ones I know of that is about ready to go in the clinical trials or is in clinical trials is a dextran-based nanoparticle, which appears to be pretty benign.

That takes us into a whole area. Right now that nanoparticle is being used to identify epileptogenic foci using MRI. It binds to the epileptogenic focus, and enhances the MRI image, and looks pretty good. The newest thing in nanoparticles is what is called (theranostics), where there are both therapeutic and diagnostic so you can be sure that you are delivering to the right cell, because it is enhancing an MRI image or whatever, and then delivering with the same particle, delivering the drug to that cell.

Cancer, (I was very) interested in it, and it is what we used to say about the gene therapy that you know, if you can use the body's response to the viral vector in gene therapy, cancer is a great place to do that. If we can, rather than just hitting a cancer cell with a bigger hammer, which is basically what the poisons are based on that we use now, if we could target using specific ligands on the surface of the nanoparticle to a cancer cell or to some other cell of interest therapeutically, show that it has gone to the right place in the diagnostic mode, and then you can deliver the therapeutic to that cell. I think this is an exciting time.

Leon Henderson: Wonderful, and you and our listeners will be happy to know that Intel will have a nanoparticle series, introduction series coming up. We were just at the San Antonio Breast Cancer Conference a couple of months ago, and we did see a lot of evidence that this area is moving forward rather rapidly in terms of manipulating the light dispersion characteristics or the light absorption characteristics of alternative diagnostics and therapeutics.

And I think we are at crossroads, and this will hopefully go forward rapidly. Do you feel that the drug delivery aspects of nanotherapy is more optimal than the delivery characteristics of – for instance, gene therapy. I know it has been – issues of not only the immunogenicity, but also delivering the DNA or RNA of choice to the appropriate cell that has been a problem. Do you think there is any time soon we're going to see those delivery issues mitigated in gene therapy, and conversely do you see a more rapid path to better delivery in nanotech?

(Edward McCabe): Well, gene therapy really involves genes by definition. The nice thing about the nanoparticles is that they can deliver whatever you load inside of

them. And so a lot of the early studies that I am aware of at least, are using small molecule antitumor drugs, but delivering them to the tumor cells and not every cell in the body, so that you really can target the specific cell types.

I'm excited about that. It is not just genes. It is also proteins and small molecules. So, I think they are more flexible as a therapeutic delivery system. (Jeff Singh) who is here at ULCA is an organic chemist and part of the California NanoSystems Institute. And Jeff has amazing nanoparticles. He has got PUP-TUP particles, where an enzyme in the cell just pops the top off and even delivery has got nanovalves that will open and shut the delivery (inaudible) over time.

They're just doing some very, very cool stuff with the nanoparticles. I think the big issue will be nanotoxicology, and I'm sure in your series you will be looking at nanotoxicology, because there are some investigators and some groups that are concerned about these things getting into landfill, getting into groundwater, and that they will have toxic effects that we can't control.

Leon Henderson: I have heard those arguments, but are these arguments any different than the original small molecules, you know, when they are first discovered. I am sure, we're going down in scale, but aren't these arguments present throughout?

(Edward McCabe): Well, I think, you know, I think we need to do the experiments, and so certainly we can regulate them, and make them safer that way. The key thing is, you know, the public is going to demand they be safe. We need to show that they are safe. Andre Nel, who is also at UCLA, and a leader in nanotoxicology, when he talks about the rate of things getting through the FDA, you just can't keep up with the changes in nanoparticles. So Andre has developed a way of saying, which are the highest risk, which are lower risk.

Let us take the high risk ones and run those through, and we can't afford to do them all in animal models. So, how can we do them first using informatics, then followed by cell culture, and eventually taking those that we are concerned about to mice or other model organisms.

Leon Henderson: Can I talk about another bottleneck. This is one that comes up from time to time, and we talked a lot about it at ASHG, and people are always asking us just where and how. Where are we in making pharmacogenetics, one, more palatable and more of a universally palatable and valuable tool, and what should we look for that will tell us that the time is now and that it is not only to keep these technologies close to the vest, but it is also to put it out there in widespread clinical use.

(Edward McCabe): Yes, pharmacogenetics, my PhD is in pharmacology, and I'm a big believer in personalized medicine. I think that pharmacogenetics is the area where personalized medicine will first be practiced. And I teach the medical students at UCLA about personalized medicine. And I point out that the driver there is not going to be them. The medical students and what they know or don't know about pharmacogenetics. The driver, I think for pharmacogenetics is going to be (lawyers).

If you look at the number of adverse drug reactions, every year at the IOM studies, other studies that come out, it is just scary. As the head of a children's hospital, I just – it is one of the things that does keep me up at night, worrying about adverse drug reactions. And adverse drug reactions are not purely (sarcastic), they are just not probabilistic. There is a subset of them that is genetic.

And we need to figure out, how we can prevent those genetic-based adverse drug reactions. Having said that, warfarin, there was just a study that came out with warfarin that showed that knowing that someone was a slow metabolizer or rapid metabolizer really didn't change the risk of adverse drug reactions.

I mean, I would not have predicted that result. And I still don't understand it. Does that mean, we don't really know how to use the genetic information, I just – I don't understand that at all. But certainly, you know, the – I have up on my computer screen, pseudocholinesterase deficiency because somebody was asking me about that, how is it relative with pseudocholinesterase deficiency, and a lot of the ones that we are aware of are in the realm of anesthesia.

Individuals who don't wake up fast enough, we're starting to see it at least in pediatric oncology, where we know that some of these poisons can be – their toxicity just increases dramatically if they have a certain genetic variant. So, those are the two areas that I see it being picked up very rapidly, and I think when we see a few more successes and the pharmacogenetic arena will catch on.

If that study on warfarin had come out of the way I anticipated it, that it would have made a big difference, you can bet that there would be ads on TV, saying if you were taking warfarin, and have had an adverse drug reaction with warfarin, call this 1800 number and we will get you a bunch of money.

Leon Henderson: It is more popular than ever, isn't it. That is an interesting situation that the driver being adversity as opposed to knowing in whom an agent might work, in whom an agent will create harm, and certainly the first effort is always to do no harm. That is very compelling, and I have to wonder and I have to amuse, well, is there any way in the FDA in this case, their risk intolerance be of utility, and are there any movements afoot to sort of actually be more proactive in that respect as an agency, and perhaps you know sort of use their conservatism in a positive sense?

(Edward McCabe): Well, I think the FDA would say, 'Hey, we did the right thing with warfarin. They were going to – they had planned that there was going to be a rule that came down, I think about a year and a half, two years ago that you had to have – if you were started on that anticoagulants, you had to have a SNP chip done, single nucleotide polymorphism analysis done within 24 hours to look and see, which genetic class did you fall into. They were lobbied heavily, and they were told, let us do this study before we make a new regulation.

They did the study and the study came out I think counterintuitively. So, they would say, 'See, we were right to listen to those people, who told us not to just make a regulation.' I think that was one where they were ready to act...

Leon Henderson: Sort of an ironic setback in this situation given what we have talked about.

(Edward McCabe): But I think, what we're talking about is personalized medicine. It is a completely different paradigm than we have been using in medicine. If you look at the latter half of the 20th century, the real successes were in epidemiology, new vaccines, better antibiotics, looking up – smoking, as another example. That was epidemiologic. It is not good for a population to have a high proportion of smokers.

Now, we are moving into a different paradigm, and it is always difficult to change paradigms. And we're saying, we are not going to treat populations. We are going to treat individuals. And for physicians to change their whole attitude towards how they are going to practice medicine is not going to happen overnight. The group here in genetics was one of the leaders in using these genome-wide microarrays, the single nucleotide polymorphism microarrays or SNP chips, and we have just developed a joint venture, the Personalized Genetic Medicine center, with pathology where we link genetic counseling with the laboratory test to help families and physicians understand how to use this powerful technology.

And I just checked in, right before our college, I checked in with the genetic counselor, who we brought on board to do this, and it is almost all, the uptake is almost all in the genetics clinic. And so we really have to get more actively engaged with our other sub specialists in genetics and then beyond so that they understand how important this is. One of the indications for using SNP microarrays is autism, because there are a number of – copy number of variants in that deletions, in general associated with it.

We're saying that any child with more than one organ system involved with congenital anomalies should have the SNP chip run, and we have got, I think, certainly tens, maybe over a 100 indications already for it, but we are not getting the up-tick outside of the genetics community because people don't understand it. We're saying, if you use to think you do a fluorescence in situ hybridization or FISH test or a karyotype, probably today you need to go to the SNP chip as the first test.

Leon Henderson: Sure, and it sounds like there is enough to get (inaudible) some good activity over this time, but what is going to be the next for not only (inaudible) and

Roche, but also Affymetrix and Agilent to move forward. It sounds like there is a lot of onus on public health initiatives to be that particular catalyst. If we had investigations that indicate almost on a (Framingham) level that the utility was across a broad swath of the population that that would be a catalyst to look for.

(Edward McCabe): And then the other thing is, I don't know if you heard this, (Dr. Henderson) at the American Society of Human Genetics, but a paper had come out right before that meeting on the dark matter of genetics. It seems like using the tools that we have available today, explains a relatively small amount of genetic variation. And so people are talking about things like micro-RNAs, and other things that we don't even know about yet, as to dark matter of genetics that, you know, it is the undiscovered stuff that we can't see that is still out there to be investigated, and then identified, and then used in a clinical setting.

Leon Henderson: Yes, you know what, you know, hold on folks, we have only been at this for 60 years, right. So, there is a lot to go, and I think this all – things are at a bottleneck in certain areas, but the promise, obviously is there, and we are looking for catalysts to take us in the right direction and a conversely negative catalyst that might detract from our goals as well. Before we turn to questions, there is one other area that I want to take a look at that is tied into some of inborn errors and orphan diseases to get back to that a little bit is newborn screening and the status of newborn screening, and how that aids us, and hopefully with the advent of specific molecular therapies for issues like (inaudible), you know, the onus is greater on both the therapeutic and the screening tool. Where do we stand in terms of newborn screening these days?

(Edward McCabe): Well, newborn screening is dear to my heart. I have been involved in it since, well, before 1976 actually. And Dr. Linda McCabe, my spouse and I wrote a book called DNA: Promise and Peril. It came out in March of 2008, and we actually argued there that newborn screening is the laboratory for personalized medicine, the newborn screening, which we have been doing since 1961, is really personalized medicine, and we followed that up with a paper more recently in greater depth in the Annual Review of Medicine, where we make this point even more.

Newborn screening is where you don't see the patient, you do the lab test. And I think there is some of that that already our patients are doing through 23andMe and some of the other direct-to-consumer testing, where they show up in the doctor's office with the lab test, and then the physician needs to interpret it for them.

But I think that we have seen expanded newborn screening, which is the addition of tandem mass spectrometry, which added 30 plus diseases with one technology. And we're going to see more of that. We're going to see more rapid acceleration of the diseases for which newborn screen can test, and I have predicted that somebody somewhere is going to start using these SNP microarrays for newborn screening.

Baylor College of Medicine is using them for prenatal diagnosis, and yet we don't understand what these copy number variations, deletions and insertions, what they all mean. Some of them appear to be just polymorphisms. We all have copy number variations. Some of them are going to modify the expression of disease, expression of genes, and the expression of the phenotype, some are going to create the phenotype.

We don't really know, and yet people are using them critically. It is a lot easier if we see something that we have seen before, and know what it is associated with. But I think there are all kinds of new technology that is going to be used in newborn screening. It really became – I was at Cleveland Clinic, gave a couple of talks up there in the fall, and they are doing something very much like a personalized genetics medicine centre.

I think the name is almost the same, Center for Personalized Genetic Medicine or something. And the group up there, I realize that, and I was doing my homework before I go to a place and start talking about personalized medicine, finding out that they had something almost like what I was going to talk about, and then realized, now they are really focused on cancer. And so they are looking at polymorphisms.

I'm a pediatrician. I don't want to know about this six-week old's risk of breast cancer., you know the American Academy of Pediatrics says, unless

you can do something about it, when you are a child, don't worry about even looking there. And what we are using, we are using the same microarrays, but we are using it to look for deletions and insertions, copy number variations. So, same technology, same name to the program, but a completely different use of that technology.

Leon Henderson (Jerrie), I like to, as we approach the close of the hour, poll for questions.

Operator: Thank you, sir. At this time, I would like to remind everyone in order to ask a question, press star one on your telephone keypad. Again, to ask a question that is star one on your telephone keypad.

We will pause for just a moment to compile the Q&A roster.

Leon Henderson: Thank you very much, and in the meantime, there is so much food for thought here, and what we are looking for are catalysts in the positive direction and in the negative direction, and we have outlined several today already. I'm curious, I want to leave it open for you. I think I have – you have usurped a lot of my time by a lot of questions, but I wanted to leave it open to you to discuss other things that you feel unprompted, excited about or perhaps that are as you indicated overhyped in the field?

(Edward McCabe): Well, I think there are some real synergies. We developed a Mattel NanoPediatrics Program here in Mattel Children's Hospital, and to our knowledge it was the first nanomedicine for children. So, NanoPediatrics and our tagline is NanoPediatrics, enabling personalized medicine for children. So, I think the real synergies between nanodiagnostics, which is what these microarrays really are, they are nanodiagnostics and personalized medicine.

So, it is an exciting time to be involved in the field, and I'm investing a lot of my energy into both nanotechnology and personalized medicine.

Leon Henderson: And this is going to dovetail into a lot of what we are going to focus on in 2010 and beyond. So, I hope you will join us again for those discussions?

(Edward McCabe): Sure.

Leon Henderson (Jerrie) have we questions.

Operator: No sir, not at this time. Again participants to ask a question, press star one.

Leon Henderson: Thank you very much. Do you have any closing remarks for us sir, Dr. McCabe?

(Edward McCabe): Well, I think that it is important for all of us to stay as on top of these developments as possible. People talk about revolution a lot, but I really think that personalized medicine going from epidemiology to now not worrying about the whole population and changes in the whole population, but how can we identify the right drug for this individual is very important. And the example I like to use is Vioxx. Vioxx was a fantastic drug for probably 98 percent, 99 percent of the population.

And then there was a group that won't even get close to this stuff. My guess is that is genetic, and we need to learn how to utilize drugs appropriately, and tailor them to the individual. If they are dangerous for that individual, don't use them. There is a whole area of pharmaceutical industry, the boutique pharmaceutical companies, that is recognizing that we need to begin to develop drugs in an entirely different way.

Leon Henderson: And I think not only these interests, but also the interests of drug developers in general, where you have an agent that could fail fast, if you will, whereas you are utilizing a lot of efforts to fail rather slowly and you save a great deal of resources, we could identify those failures a little bit earlier on in the game, and I know that is a lot of discussion going on this year. So, I think this year, we're going to be focusing not only on nanotech, but also fail fast strategies, other catalysts, including newborn screening, especially in CF, DMD and others, and our continued series on single gene disorders and their therapies as some of the chaperone and other therapies come forward as well.

(Jerrie), if there are no further questions, we will conclude our discussion, and I will thank everyone for joining us.

Operator: Thank you, sir. There are no further questions.

(Edward McCabe): Thank you.

Operator: This concludes today's conference call. You may now disconnect.

END