TRANSCRIPT

Progress In CD: An Update On The Advances In Crohn's Disease

October 6, 2010

Slide 1: Progress in CD

Operator:

Hello, everyone, and welcome to *Progress in CD: An Update on the Advances in Crohn's Disease,* a telephone webcast education program. It is my pleasure to introduce your moderator, Kimberly Frederick, Vice President of Patient and Professional Programs at the Crohn's and Colitis Foundation of America.

Kimberly Frederick:

Thank you. On behalf of the Crohn's and Colitis Foundation of America, welcome, everybody, and thank you for attending today's program, which is sponsored by Centocor Ortho Biotech.

This is our first program targeted solely on Crohn's disease, which we were able to offer based on what you, our participants, wanted to hear. And in order to help us guide future program topics, we'd like to encourage you to fill out the program evaluation form, which is available online or in your registration packet.

We'd also like to thank everyone who submitted questions in advance of the program. We have worked really hard to address many of those in today's program. We will also have an interactive question-answer session following Dr. Braun's presentation. We will take as many questions as time allows from both the telephone and webcast participants. If we are not able to take your question, please contact our Information Resource Center at 888-694-8872. The Information Resource Center is open Monday through Friday from 9 AM to 5 PM Eastern Time. And if you don't have access to download the program slides, you can contact our Information Resource Center and they will be able to provide them to you.

If you know someone who's missed today's program or want to refer to it again yourself, there will be an interactive archive of today's program posted on the CCFA website, where you'll be able to listen to the presentation, view the presenter's slides, and download today's transcript.

Slide 2: Jonathan Braun, MD, PhD

And now it is my pleasure to introduce Dr. Jonathan Braun. Dr. Braun received his B.S. from Stanford University and continued on to Harvard Medical School, where he received his MD and PhD. Dr. Braun completed his residency in pathology at Brigham and Women's Hospital and completed a postdoctoral fellowship with David Baltimore at the Whitehead Institute. Dr. Braun then joined the UCLA School of Medicine, where he is today. Dr. Braun serves on the CCFA National Scientific Advisory Committee, President of the Clinical

Immunology Society, membership on several editorial boards and NIH Advisory Panel, cofounder and president of the Federation of Clinical Immunology Society, a leading international organization for translational immunology. Dr. Braun's research centers on the mechanisms of microbial immune commensalism and conflict in the intestine, the molecules and cell biology involved in this interaction, and the related search for new strategies of diagnosis and treatment of inflammatory bowel disease.

And now I'd like to turn the time over to Dr. Braun.

Dr. Braun:

Good afternoon or good morning, depending on your coast. It's so nice to have the opportunity to speak with all of you on behalf of the CCFA.

It's been a particularly exciting year, perhaps the most eventful year, for Crohn's disease research that I can recall. And so I feel a bit like having the end of a great day, this great year, and to be able to gather around the kitchen table with family to reflect on what's happened. So with your coffee cup in hand, let's talk about what's happened and how it relates to understanding the disease and approaches for treatment.

Slide 3: Crohn's Disease

Crohn's disease, I'd first like to introduce for those of you who are not fully familiar, although I know many of you are, is a chronic disease of the intestines. If you were to look at the intestines, you'd see that they are affected by sores, sometimes even holes, perforation and scarring and fibrosis strictures, which result from this chronic inflammatory disease. It affects all parts of the intestine and the experience of a patient having this are periods where one is affected by a great deal of abdominal pain, diarrhea, bleeding, malabsorption, inability to get nutrients, so that you lose weight and are weak, and other complications like abdominal infections or elevated risk of cancer. So these are serious diseases – this is a serious spectrum of disease.

What I've shown here is what it looks like under the microscope, where the disease is diagnosed. Here's the normal intestine, where the food would be located out here. This is the lining of the intestines, where the absorption takes place. And the little while cells here which are secreting mucin, which I'll tell you about in a little bit. This is the normal. In the middle panel you can see the inflammation, where it now becomes red and swollen and there's an area of bleeding and tissue breakdown. So this is when the disease is active.

After effective treatment takes place, then the intestine can be restored to normal health, and the big excitement has been to understand what causes disease activity to take place and what treatments we can use to either prevent that damage from taking place or to reverse it to this normal state.

Slide 4: Crohn's Disease

If one were to look by endoscopy, where a tube is inserted from the anus and then by observing it fiber-optically, looking at different parts of the intestine, you could also see what the intestine looks like just by viewing it. And I think you could appreciate where this is mild-colored normal surface of the intestine, that here you could see redness or areas of bleeding or tissue breakdown. And this is features of it, that the gastroenterologist would see when you have that type of examination.

We know that the peak onset of the disease is, when it first presents itself, is often in the teens, although all ages are affected and there is – and for people that have it when they're young children, it will affect growth and development.

We know that it's immune-mediated. We know that in many cases there's a family component, which makes us believe that it's genetic. And that finally, that there is an environmental effect. And there's been a great deal of advance in understanding what that's about, which I'll tell you in a minute.

So what we're going to do now is talk about three areas of research advancement, about genes, about intestinal stress and about bugs. So let me take you through those three areas.

Slide 5: List of CD Genes Is Expanding

First let's talk about genes. At the beginning of this decade, there were the first two genes which were discovered that were associated with Crohn's disease. You can see the two here in the middle of this panel. But it was up to eight genes in 2007, 32 genes in 2008, and now this past year we have approximately 70 genes which are either certainly or likely to be associated with disease risk.

Now that we've identified so many genes, we've learned that they fall into three categories. They either affect immune regulation, the ability of the intestine to serve as a barrier to protect us against bacteria and other insults that are damaging material that's present in the food that we eat, or that there are deficits in genes involved with the policing of the bacteria that live in your intestine.

Slide 6: What Do CD Genes Teach Us?

The issue has been to understand how we can use those genes. First of all, although there's been a large increase, we know that there's a lot more genes to discover, the estimate now is there's going to be between 200 and 400 total genes when the studies are done.

We also think that patients don't have all 200. They're just going to have, any one patient or their family, will have five or ten genes, which will be their risk. Now that has two implications. One is that among other family members, the ones which are unaffected may be so simply because they happen to have gotten slightly fewer number of genes than family members that were affected. So you need to have a sufficient number to put you over the top and get into trouble. The other point is that if that's the case, then that means that just like unaffected brothers and sisters who don't have the disease, you don't need to fix all of the genes in order to get you out of trouble with your genes. You just need to fix one or two.

Slide 7: Immune Regulation

Now we've tried to understand, by looking at individual patients, what are potential genes which specifically affect intestinal risk and it doesn't mean – and what we can do about it in terms of targets for therapy. So let me give you two examples with regard to immune regulation.

There are hormones which affect the immune system and one of them, which is interleukin-10, which is a peace-keeping hormone, which keeps things quiet in the intestine.

Slide 8: Early-Onset Aggressive CD

And there was just the discovery this last year by Scott Snapper, who's a CCFA

investigator, and in fact the head of our research initiatives committee, he and his team reported that there were rarely patients who had Crohn's disease because they actually had a defect in this peace-keeping hormone. And here I can show you what it looks like. Here is an endoscopic look at the intestines, where you can see that there's a sore and there were also other problems such as skin rashes and the like. This is an unusual form of genetic risk, but what was interesting is that by knowing exactly the nature of this genetic disorder, Dr. Snapper and his team were able to select a specific way to treat it, which in this case is to use a stem cell replacement. And in two of the patients that had this form, genetic form of disease, that did create what turned out to be, what would appear to be a cure.

I'm working with the slides, I'm sorry.

Slide 9: Targeting the IL-12/IL-23 Pathway

What I want to share with you is another hormone, which is also important for immune regulation, but in the other way. This is a hormone called IL-23 or IL-12, which activate the immune system and in doing so it creates greater immune activity. And so in this case, although this was discovered in animals, just about two years ago a group of investigators led by Judy Cho, also a CCFA investigator, discovered that this was a common genetic problem in Crohn's disease. More than 90% of people with Crohn's disease, one of their genetic problems is that they have an overactive receptor for this immune hormone, this activating hormone. And so this suggests that a possible treatment would be to reduce the activity of this hormone by using a neutralizing antibody. That was tested about five years by Peter Mannon and his team that was reported in the New England Journal, which found that a neutralizing antibody against these activating hormones was able to reduce the disease activity and give benefit to patients.

Now there is a clinical trial going on with the current form of that neutralizing antibody, which is called ustekinumab. And so we'll be knowing in the next year or so whether that treatment is going to be effective. And if so, that will be exciting, because it will be a totally new way to treat the disease and it should benefit the majority of people with Crohn's disease.

Slide 10: Barrier Control and Epithelial Stress

So I've just told you a little bit about immune regulation and genetics. Now I want to tell you about the intestinal barrier in genetics.

The intestine is lined with a layer of mucus, which is shown here in green. And when I say mucus, it's almost identical to the type of mucus that is present in your upper airways and in your nose, when you have a cold, and you sneeze and the mucus comes out. The body uses mucus to create a barrier, it protects us from microorganisms. And in the intestine, shown to the far right here, the layer of mucus is thick with actually two layers. A layer, which is deep and which is the insulation layer, which is very thick; it keeps the bacteria total out. And a more superficial layer, which is looser, and really forms the type of flypaper to which the bacteria stick and prevents them from getting inside of our bodies. So that's how mucus works. And I've shown you what I think is an interesting picture. This is actually a molecular microscope viewing, where the bacteria are illuminated in green and you can see them present in the loose layer, where they're stuck onto this loose layer of the flypaper form of mucus, and then the deeper layer, which is the insulation layer, which is only green, that's the mucus, and there's no bacteria there, so you see no orange. So this is the flypaper or insulation model of barrier control in the intestines.

Slide 11: Deficiency

Now the recent work has asked whether there might be genetic problems in this mucus layer, which would account for disease susceptibility. And just two months ago, Dermot McGovern and a national group, which, around the United States, studied people with genetic risk of Crohn's disease and found out that it was actually fairly common, that there was a problem with the flypaper part of the mucus. The flypaper is formed by sticky stuff, formed out of sugars, and one type of glue is called fucose. And that's indicated in this red triangle.

So what happens is that in many people with Crohn's disease, they have a genetic variant which prevents them from putting on this sticky fucose molecule. And as a result, you have a different type of sugar structure, which doesn't properly attach the bacteria and allows them to invade. So whereas under the normal circumstances the intestine is protected from bacteria, in the case where you don't have good flypaper, the bacteria are able to get in and then elicit an inflammatory response.

So this was I think an important finding because it suggests that if we were to then create a proper sort of mucus that could presumably be produced as a pill, then that would replenish the proper form of the mucus and those are studies now being done in animals and we'll know pretty soon if they're effective in that setting and whether they could be safely used in patients, which will be what will be ahead.

Slide 12: Cellular Stress

The next area, and the final genetic area I want to share with you, is about stress. Now we all know about the psychologic experience of stress, but at the cellular level there's also an equivalent of that, called molecular or cellular stress. This is induced by lots of things that the intestinal lining can encounter – the bacteria which are living in the intestinal lumen, eating our food, but also other things, viruses, or toxic substances like smoking or aspirin, which we know are a significant stimulus for flares of Crohn's disease.

Now there's been a lot of work done on the way in which the cells in the lining of the intestine respond or are able to adapt to stress. And this molecular system is called the UPR system and induces a number of things that cells do to compensate and prepare themselves for the molecular stress of these sorts of insults.

Slide 13: CD Risk

What's been really exciting during the last year is we've learned several genes, which are involved in that stress response, which are somewhat defective in patients with IBD or Crohn's. So I've indicated a few of them here, where in the red are genes which are specifically affecting Crohn's disease, and then in the blue are genes which affect several forms of inflammatory bowel disease, Crohn's and ulcerative colitis. And these are all genes which affect different parts of the molecular stress response. So if you're missing one of those genes, you're missing part of your ability to adapt to stress. And so the cells break down and barriers and sores start to form in the intestine because they can't withstand that sort of damage.

Slide 14: Stress Therapy

Now what's exciting about that is that this gives us a new idea about thinking about how

people get Crohn's disease. So in addition to the immunoregulation problem, with regard to stress, this means that if you have these genetic problems, than rather than having this case where you're in the yellow zone, where there's a lot of ability to respond to stress, that you're further along towards the right, where your ability to deal with stress is poor and so you start to get these problems related to cellular breakdown.

Slide 15: CCFA Genetics Initiative

Now what's exciting about that is some of these ways that cells start to get into trouble from stress can be treated with particular sorts of drugs. And so the goal now is to consider ways in which we can intervene. And so as a result, the CCFA has done two sorts of initiatives on genetics research. One of them was done ten years ago, and this is CCFA's effort to begin to look at the genetic problem in Crohn's disease. And what I've been telling you is the result of that sort of research. We gathered together the first international team, looking at the genetics of IBD. We created unique resources for doctors and scientists to study. And many of the genes, which I've described to you, are ones which came directly out of CCFA-funded research.

Now that we have our 70 genes and many more accruing, we are starting another phase of research, where what we want to do is to create two things, to actually bring this into treatments, or even the possibility of cure.

One of them is to create a toolkit, a dashboard for genetics, which patients and doctors can use, so that you know what are your five or ten genes that are your problem. If you can know exactly which ones those are, then that will give you a very specific idea of what treatments might be targeted towards you particular problem.

The second is that we want to continue looking carefully at the genes, to find the ones which are most likely to affect disease, either respond to treatment or your level of disease severity. And if we could find those genes, then we will focus on those to find the ones which are most suitable for treatment.

That is the work of the second phase of the CCFA's genetic initiative and we're working hard to develop that in terms of the funding for it, and also for focusing our doctors and our scientists to join in on that effort.

Slide 16: Agents in the CT Pipeline

Now let's talk about treatment for a moment because many of the treatments, which are presently in the pipeline, are the result of the genetic research or animal research, which is related to what I was describing to you these last few minutes.

These include drugs like the TNF blockers, infliximab and adalimumab, which are widely used, but also other categories of biologicals like homing blockers, natalizumab, which has just been approved about a year and a half ago, and others in this category. Blockers for activating hormones of the immune system, and I told you about IL-12 and IL-23, that's now in clinical trials and we should know in a year or two how safe and effective those will be.

There's other quite exotic, but exciting studies going on, like the use of mesenchymal stem cells. Many of you have probably heard about stem cell research and that is being looked at right now as a therapeutic approach in IBD. And there's one clinical trial which is going on right now, which I've listed here, and we'll know probably in about two years whether it's effective or safe.

Finally, with so many drugs presently being used, one thing we don't know is which combination of those drugs might be particularly effective. So that is an important question, which needs to be studied in order to guide doctors and patients on how this should be done.

During this last year two papers, one from an American group and one from a European group, reported that a combination of TNF blockers and methotrexate are more effective, than either of them alone, for treating patients with very severe Crohn's disease. So that was an important advance. However, we also learned that there was a small, but detectable rate, of complications such as a greater risk of infection or even cancer risk. So this was an important piece of information, which is now going to be available to patients and doctors to make decisions about the best way to the advantages and disadvantages of combining these drugs.

The work right now is to look more carefully at other combinations. And the clinical alliance of the CCFA is doing studies to look at these combinations, to give more information to guide those decisions.

Slide 17: IBD Epidemic

Now let me turn to the question about bacteria in IBD.

We know that IBD is an epidemic. Since World War II the incidence has increased more than 20-fold. And it's also spread around the world, whereas before it was just in Europe and parts of North America. It's now spread to Southeast Asia and other areas. And we're pretty certain that that's because of changes in the environment and lifestyle that are affecting disease risk. But what we need to understand is how that would go, in other words, what's the mechanism.

Slide 18: Injurious and Protective Bacteria

And the most likely – one of the likely targets of that is bacteria. And the reason for that is because bacteria eat what we eat. And so if we change our lifestyle of our diet, if we also change the environment around us, then the bacteria that we encounter are different and they could affect our health.

Slide 19: Individual Variation in Microbial Composition

There are a lot of bacteria in our bodies. We have a trillion human cells in our body, but there are almost 100 trillion bacteria. So on a percent basis, we're only 10% or 1% human. So these bacteria are very important to our health.

The CCFA two years ago, recognizing the importance of this, established a large project to study bacteria and to ask what are these bacteria, what are they doing inside of our body and how can we study them.

Slide 20: CCFA Microbiome Initiative (1st phase)

And what that project has taught us is that there are more than 200 species of bacteria in each person. There's little overlap of bacteria from one person to the next, so we each have our own fingerprint. Although interestingly, you get your bacteria mainly from your mom and as a result you and your brothers and sisters and your mom will share bacteria. So that gives us a very surprising insight about susceptibilities or resistances to disease that would be related to the family structure.

And a fantastic toolkit, called the QIIME toolkit, has been created by this initiative, which is a research and potentially a clinical tool for individual patients, to be able to monitor their bacteria.

Slide 21: CCFA Microbiome Initiative (2nd phase)

So what we're doing now is starting a second phase, where we want to ask a number of questions. What are the bacteria that distinguish people with inflammatory bowel disease as opposed to the healthy state? What are those bacteria doing and what can we use to change the bacteria from a disease state into a healthy state? And so we'll be looking carefully at questions which are on many people's minds, like whether diet or probiotics will have an effect, antibiotics, or other ways to manipulate the bacteria in our body. Right now we don't know the answer to that, but there was a study that was just funded, initiated, with $6 million of Crohn's disease funding to gather together a group of investigators to give us that answer.

Slide 22: PRO-KIIDS

A study which will make that possible is to look at individuals that have the disease at a stage where it's particularly informative. And we know that children are a very important group of people with Crohn's disease to study. There's two reasons for that. One of them is that those are people that have just gotten the disease. So if there's a chance to identify the factors, which have caused the disease to be triggered, children will give us the best chance of our answer. The second is that Crohn's disease is particularly severe in children. When you get it as a teenager and an adult, it is less likely to be as severe as it will be if you get it when you're a younger child. So CCFA, recognizing the importance of this, and the severe effect of it on the growth and social development of children, we decided to establish a network of investigators around the country to study kids with this disease. So it's a large CCFA commitment of more than $5 million. And during this last year that study has gotten started. Started with 10 centers, we've already activated 38 centers, and our goal is to have 1,100 children with new-onset Crohn's enrolled into this study so that we could identify their environment, the diet that they're eating, their genetics and their bacteria, so that we could understand how all the factors come together, to determine the nature of their disease, how they respond to treatment and what could we do to help them.

Slide 23: PRO-KIIDS

The study will be occurring in about three years, and we'll be particularly interested to see how these different factors affect the complications of disease, in other words, whether they have an easier course or more severe course, and whether they have to undergo surgery, which is one important indicator of how bad their disease is.

And so that will be going on and I encourage you to be in touch with your local doctors to find out whether your doctor is part of that network. Because if you have a member of your family with a new onset of disease, your family could be an important partner for that research.

Slide 24: CCFA Partners

And in that context, I want to share with you a broader initiative. We know that this is a disease which affects patients and the risk is actually in a family. And so in order for this to be studied, although we could learn a lot from studies in the test tube and studies with animal

research, we know that we have to study very carefully people with the disease. This means that we have to have a partnership of individual patients and their families, who are willing to step forward to share with us the information about their disease, biologic specimens that could be used to study these different aspects of genetics and bacteria, and to participate, where it's appropriate, in clinical trials.

Because the CCFA is the single largest gathering of people with this disease in this country, we realized there was an opportunity to create an active partnership, where patients, doctors and scientists, all together as a team, to study these issues. So the CCFA has initiated a project called the CCFA Partners Project, which is directed by Lloyd Mayer, Bruce Sands, Jim Lewis and Sunanda Kane. That project is to engage people that are willing to step forward to be part of this partnership. If you'd like to learn more, I'd encourage you to take the opportunity to do so by getting in touch with the information line at the CCFA, which is listed with info at CCFA.org.

So let me thank you all for listening to my comments, and I turn it now to our moderator.

Slide 25: Questions & Answers

Kimberly Frederick:

Thank you, Dr. Braun, for that really informative presentation.

We're now going to begin the question and answer session with the audience. We know that many of you have questions and we'll address as many as we can. To help us, we will limit questions to one per person and ask that your questions be general in nature and not specific to individual cases.

Dr. Braun, I'm going to ask our first question from the web audience, and it's from Anna. Her question is, "Are there standard blood tissue tests available to patients to identify which or how many of these genes are involved in an individual and that can pinpoint the current/future severity of this disease?"

Dr. Braun:

That's a great question. Now that we have a significant number of diseases identified, there's something called the immuno-chip, which is still a research tool, but a high throughput and fairly low cost tool, to test for variants of – quite a few of the genes which are associated with IBD.

Here's the difficulty, though. Right now, though the information from that chip doesn't really give the patient and the doctors more information than knowing that you have a risk of the disease. In other words, it doesn't tell you specifically what your severity will be like or what sort of treatments would be most suitable. So the effort now is to create a larger chip and get more information about the genes, so that when the genetic information is made, that we'll be able to get that sort of information.

So I'd say that the question you're asking about, the studies for the second generation chip are just going on now and if we were to talk in another year or 18 months, I think that there's a good chance that we'll have a chip that will begin to give that sort of information.

Kimberly Frederick:

OK, great. I have another web question. It's from Keith. "Your talk suggests that all

patients with Crohn's disease should have their genes mapped for these genetic problems. Should patients do this?"

Dr. Braun:

Again, the issue there is that there's two problems. One of them is that just getting the genes mapped doesn't right now give us much information on how to treat. So today it would not be useful to you or your doctor to get your genes mapped. Again, in about a year or two years we'll know enough about the genes that we'll be able to – that in getting the gene list for an individual patient, we'll be able to give some specific recommendations of what treatments to try or not or how to predict severity. So today the information would not be useful clinically, but in a year or two years I think it'll start to be.

Kimberly Frederick:

Okay, we'll take a phone question.

Operator:

Your first question from the phone line comes from Rhonda from Delaware. Please proceed.

Rhonda:

Dr. Braun, mine is a two-part question. This is concerning a current medication, 6-MP. Can a dose lower than what is typically recommended be effective for patients? And are the more serious side effects dose-dependent and also dependent on length of time that a patient is on the medication?

Dr. Braun:

Ok, great. Well, 6-MP, and a closely related drug called Imuran®, are commonly used for IBD, and it's a very good drug. The thing is that people because of – actually it's because of their genetics – are more or less sensitive to 6-MP. So right there are some very good tests to determine genetically whether you're a more or less sensitive person. By getting that testing, you could better – or your doctor could better determine whether you should be at the higher dose or the lower dose, and also which one would be safer for you.

Kimberly Frederick:

We'll take another phone question.

Operator:

Your next phone question comes from the line of Wendy from Florida. Please proceed.

Wendy:

Hi. I wanted to know about the effects that you might know of in terms of menopause and getting hormone replacement through that and the effect on Crohn's disease for that.

Dr. Braun:

I'm not aware that there's a particular effect of menopause on disease activity. So there are significant changes in activation or quiescence of the disease, but to my knowledge that is not specifically related to menopause. But it's important to continue to recurrently be in touch with your doctor to monitor your disease, so that you make sure that you're keeping it under control.

Also as people live decade by decade with Crohn's disease, you're at greater risk over time for getting intestinal cancer. And so it's important, as you get older, to be monitoring your cancer risk because you're at greater risk for intestinal cancer with Crohn's disease. So menopause means that you're getting somewhat older and that would be a reason to be, if you're not already doing surveillance, regular surveillance for intestinal cancer that you're doing.

Kimberly Frederick:

A web question. There were a few along these lines, so I'm going to ask the one from Amy. "Please say more about the Mom bacteria connection."

Dr. Braun:

Right. When you're born, when a child is born, it's sterile, there are no bacteria in the body because the uterus, the womb, has no bacteria in it. When the baby comes out and it encounters the world, and then all the bacteria rush in. They're supposed to do that because we need bacteria to help digest our food and to help keep the bad bacteria out and so on. And so it's a natural occurrence. Where did the bacteria come from? Well, they don't come really from the air because there's very little bacteria in the air. They come from contact from caretakers. And so in most societies Mom is the intimate caretaker of the child. And so during those first days, weeks and months, Mother is the main contact person for the child, and so most of the bacteria that come in are acquired from the mom.

Kimberly Frederick:

Okay, we'll take a phone question. Hello?

Operator:

Your next phone question comes from the line of Jane. Please proceed.

Jane:

Hi. My son is on Remicade®. He has had Crohn's for over 10 years now, and he's been on 5 milligrams of Remicade for almost two years and he is doing amazing on it. All of his vital signs are well and he's feeling great. And our concern is what are the long-term effects of being on this? Obviously there are a lot of side effects, which he has not experienced yet, but we're concerned about the risk for leukemia, cancers, infections, and have they done any studies, because it came out in the 90s. And also he's getting a colonoscopy in a couple months, they do follow up with colonoscopies every year.

Dr. Braun:

First of all, the biggest risk in Crohn's disease is the disease itself. So finding a treatment which commits excellent control of disease is terrific. And so that immediately is great news. And if he's benefitted for 10 years with infliximab, which is the generic term for Remicade, then that's

wonderful.

There have been studies about risks. We know that there's a slightly increased susceptibility to certain forms of infection and certain forms of cancer. Interestingly, you see that mainly in the first year or so of treatment, and then it seems that you stabilize out. So that's good news. As you say, we're all just experiencing the first generation's use of infliximab. And as we do, we'll find out more about what benefits, additional benefits or additional risks there are, so it's important for him to be in touch. But I would say for right now, if he's getting good control and if he's being monitored carefully, then that sounds wonderful. It sounds like he's a very TNF-sensitive person and so this is in effect normalizing him into a good state.

Kimberly Frederick:

Question here from the web from Jessica. "Inception of Phase II CCFA genetics initiative begins next year. Approximately how long until patients can expect to gain access to genetics toolkit?"

Dr. Braun:

Right. Well, that project will take about two years to gather enough information, that the research will tell us two things. One are what are the most useful genes to follow because a lot of people are carrying them and because they're strong predictors of disease severity or response to treatment. So we have to gather that information and it'll take about two years to do that.

Making the test is actually very easy. You can buy a test today. You can get your whole genome today done for $1,000 to $10,000. What we don't know is what those genes mean. And so that's what the study is about. So that information will give us the toolkit and the information behind it, so that there'll be recommendations that will go with the particular gene variants. So about two years, I think it'll start to be finding its way into clinical care.

Kimberly Frederick:

Okay, we'll take a phone question, please.

Operator:

Your next phone question comes from the line of Gary from Colorado. Please proceed.

Gary:

I had a question about bacteria gathered – I know you don't want personal questions, but my son and I were camping and at the start of his Crohn's disease he was drinking water out of a creek that had, I believe, beaver feces in it. I can't remember what the bacteria was identified and called. But I just wondered, is that a possibility, instead of being genetically acquired? Maybe just acquiring it through some bacteria?

Dr. Braun:

We've learned that the bacteria in your intestine you acquire mainly during the first year or so of life. And after that it becomes a very stable community of bacteria that really don't change much. Even antibiotics don't change it much because if you take antibiotics, it's just like mowing the lawn. You mow the lawn, but then it comes back and there's that little area with the

clover and the little area with the dandelion and they just come back again. So I would not take the view that a particular encounter after the first year or two is having a big change, a significant change in that. But we are learning that the bacteria you acquire early on do have an effect on your risk of IBD or how severe it would be, and that's what our current research is doing, to find out which bacteria are the ones that are having those effects.

Kimberly Frederick:

We're going to take a web question asked by Reid. "I know thousands of people all over the world use diet and supplements to bring Crohn's disease into remission for at least five plus years without any medication. Why aren't GI doctors recommending diet and supplements as valid treatment options?"

Dr. Braun:

Right. Well, I think most doctors and scientists believe that diet and supplements will in the end be very valuable. Here's the problem. There have been a number of serious studies of different diet and supplement interventions. And what we've learned is that any one intervention doesn't help – helps hardly any individual people. And the reason for that, we think – so we're very surprised by that. We believe that some individual patients will benefit from a particular diet, a particular probiotic. But because each person has a different mosaic of bacteria in their intestine and because each person has a different mosaic of genes, the bacteria, the diet or the supplements that will be helpful for one person will not be helpful for many others or maybe even deleterious for many people.

So in order to make this into something reliable, we need to get more information about the bacteria and the genetics, so that with that information we could say well, because you have these three genes and those four types of bacteria, then this particular diet is likely to really help you, but that sort of diet is going to probably make things worse. And that's what we're going towards.

So I think the idea is the same, but it's incorrect when one looks at the actual studies of this, that any one diet has really been beneficial for a lot of people. So more work to be done.

Kimberly Frederick:

We've received this question a couple of times in the IRC from people and so this question is timely, I believe, Dr. Braun. "Do you have an opinion or response to the TV commercials claiming Accutane® has caused Crohn's?"

Dr. Braun:

That's important point because Accutane is a commonly used agent for acne or for treatment of different cosmetic conditions. The studies – and Bruce Sands did a large study of this – would indicate that Accutane does give a slight risk of IBD. It's a slight risk, so it's not a major factor for the disease burden of Crohn's disease that we have. However, it would indicate that it would not be a recommendation to use Accutane if you have IBD or if you have a family with risk of that. And if you are going to consider doing that, you should certainly talk with your doctor before you choose to use Accutane in that setting.

Kimberly Frederick:
Thank you. We'll take a phone question, please.

Operator:
Your next question comes from the line of Joan from Florida. Please proceed.

Joan:
I think it's wonderful. Could you tell me, please, I know you said it's spreading and you believe a lot of this is environmental, but is there a hereditary component attached to it? Could it be – are there people that have certain genes that are more likely to have it than not?

Dr. Braun:
Yes, we know that there's a substantial hereditary component to Crohn's disease. It's estimated that about half of the risk you have from your genetics that you get, hereditary from your family, and the other half is environmental, of which we think the particular makeup of your bacteria is one important part.

Joan:
Could it be a Jewish genetic disease or a black genetic disease or an Arabic genetic disease?

Dr. Braun:
Well, there's two ways to say it. Each ethnic group has, just by the nature of the mosaic of each ethnic group, there are certain genes which put you at risk for IBD and other genes in that group that actually protect you. And so there's a lot of genes which overlap for everybody, but there are some which are distinctive, say, there's a greater risk of inflammatory bowel disease in people from Eastern European Jewish extraction. And the pattern of disease in African-Americans is different, so there must be some genes which are modifying the features of it. So yes, there are going to be ones which are shared among groups, ones which are shared among everybody and ones which are unique features just for individual families. That's why we need the gene chip.

Kimberly Frederick:
Here's a question from the web from Louis. "If we get genetic testing and are predisposed to the disease, will insurance companies deny coverage for it later on?"

Dr. Braun:
That, of course, is an important question for any sort of disease, not just inflammatory bowel disease. The current healthcare legislation in Washington, which has been passed and is now going on a year, one of its cardinal features, most important features, is that it will prevent insurers from blocking access to care because of preexisting conditions or susceptibility. So I think actually national policy, which has just recently been adopted, will make that less likely a problem.

Kimberly Frederick:

We'll take a phone question now.

Operator:
Your next question comes from the line of Myra from New York. Please proceed.

Myra:
Hi, thank you, Dr. Braun. My question was about drugs, which my son takes, it's sulfasalazine along with the antibiotic of Bactrim®. Now that's the only thing that works, these two things together. My question is how safe is it to be on long-term antibiotic?

Dr. Braun:
There's a lot known about the safety of those agents and there are people that are on it for a long period of time, so categorically, that is something which is appropriate to do in consultation – you know, and ongoing monitoring with your physician.

Myra:
So I have to be on top of it, you're saying.

Dr. Braun:
Any treatment of that sort should be monitored, yes, but there are many people that are on long-term care with those agents. So that's something, though, that should be followed with your – any sort of chronic disease, and IBD is a very important one, should be monitored carefully to watch for side effects and to make sure that the treatment that was working well last year is still working well this month.

Kimberly Frederick:
This is from the web from Ronnie. "Does breast-feeding transfer bacteria to the child?"

Dr. Braun:
No, well, only in a small way, that most of the sharing of bacteria between the mom and the baby is from the skin. So whether it's from the skin of your hands or from your lips or from the breast, a lot of it is coming from that source. So there certainly isn't – the breast-feeding as exposure to bacteria is not different from what the children – what we do know is that the profile, that because of the substance in the milk, different bacteria get a foothold early and actually more beneficial bacteria. So if it's possible, breast-feeding promotes a better profile of bacteria, at least earlier on. So if anything, that should be promoted.

Kimberly Frederick:
And this is from Jen from the web. "Should my child that is on Remicade be tested for cancers and how?"

Dr. Braun:
The decision about how to monitor for cancer surveillance is really something that should be done with your doctor because it's affected by the exact nature of your Crohn's disease and

how long you've had it. Age is certainly one factor, but duration and severity are others. So the decision about when and how much to do surveillance should be recurrently discussed with your doctor.

Kimberly Frederick:

We'll take a phone question, please.

Operator:

Your next question comes from the line of Deborah from Massachusetts.

Deborah:

Doctor, my husband is currently on Cimzia® and is not doing well. He's taken it for three doses. Prior to that he was on Humira® and didn't do well on that. He did do well on Remicade for eight years and then had a flare-up. We're at a scary crossroads now. He's almost 63 and he's had the disease since he was in his 20s and we really don't know where to proceed now. Do you have any suggestions?

Dr. Braun:

I'm glad to hear that he's had benefit before. I can certainly understand that it's an anxious time now. There are a number of choices ahead. There are other biologicals besides TNF blockers to consider that are approved. There are also combination of drugs like methotrexate and infliximab, where together, for some patients they do a better job than either of them alone. So there are – fortunately, the pipeline has created additional choices from the ones that you've described that you should discuss with your – your family should discuss with the doctor.

Kimberly Frederick:

We're going to take a question from Stephanie from the web. "Since hormones are involved, are Crohn's disease patients using birth control pills, potentially aggravating their symptoms?"

Dr. Braun:

No, they're not. The hormone that I was referring to is a special class of hormones, not the ones like the male and the female hormones, which are what – of course, the female hormones are the ones which are in birth control pills. But it's another class of hormones, totally different, which are hormones that are immune system hormones. So there was a recent study, called the PIANO study, that was initiated and carried out by the CCFA, which asked what were the risks of pregnancy with IBD. And what we learned is most everything about the state of pregnancy or treatment of IBD and its effect on pregnancy were okay. So the young woman has a – there's a lot of positives for a young woman to be aware of in terms of her disease and how she could deal with it in the context of her own biology.

Kimberly Frederick:

Here's another web question from Amy. "Is anyone conducting research into a connection between Crohn's and other autoimmune diseases?" And the example she gives is her son has

Crohn's and she has MS.

Dr. Braun:

Right. Because there's a lot of work on genetics in other autoimmune diseases, including MS, that geneticists working on these different diseases are sharing their information all the time in an orderly manner, to find out whether there are relationships. What we've learned so far is that the one overlap – there's very few overlaps with MS and Crohn's disease, although one of them is the IL-23 receptor. And so that might be a possible link. There are other autoimmune diseases, though, which have a bigger overlap, such as rheumatoid arthritis and Crohn's disease. So yes, that's a very important area. And that also means that things which are studied – genes which are identified and clinical treatments which are identified in Crohn's disease, may actually be beneficial for other autoimmune diseases and vice versa, but they'll have to be properly matched with the underlying genetics which are shared.

Kimberly Frederick:

Okay, and we'll take a phone question, please.

Operator:

Your next question from the line of Barbara from Massachusetts. Please proceed.

Barbara:

Hi. My question concerns when you have Crohn's disease and another major disease such as diabetes 2, what role in treatment does it play like in diet? What is good for one isn't good for the other disease.

Dr. Braun:

Right. Well, right now in a general sense there is no specific recommendation for diet for Crohn's disease, although individual patients might observe that certain things that they eat make them feel better or worse. So these are two complex diseases and so it's important to have doctors which are expert for the care of each of these diseases and make sure that those two doctors are talking to each other, so you can coordinate plans for treatment. And particularly drugs which, because of the nature of one disease or the other, they might have interactions that should be carefully managed.

Kimberly Frederick:

Okay, I'm going to ask you this question from the web from Paul. "Can you talk more about the environmental triggers, what might these be? I know you listed some of them, I don't know if you want to reiterate those or share more."

Dr. Braun:

The problem is that we know that urban Western lifestyle is the big environmental descriptor for IBD risk. The problem is that there's so many things in urban lifestyle, is it buying an iPad, is it driving to work, is it certain things that you eat? We just don't know. And that's been what's been so challenging. So the pediatric network study is looking very carefully at all

the aspects of the environment that kids are living in, to try and use that opportunity to learn more about environmental factors, which are the specific ones, which are affecting disease risk.

Kimberly Frederick:

Okay, and another question from the web from Ashley. "Prompted by this session, I would like to discuss advances and new research with my GI doctor. What is the best way to start this discussion?"

Dr. Braun:

Well, I would suggest going to the CCFA website because there are a number of short, but informative, summaries about what's going on in these areas. It's put together by the leading experts, so I think it's the best summary of where things are. And both you and your doctor could look at it, you could ask your doctor to take a look at it when he or she has the opportunity. Give them a few weeks to get up to speed and then do that in advance of your meeting, and then you could have something shared to talk about in a specific way.

Kimberly Frederick:

Okay, we'll take a phone question.

Operator:

Your next question comes from the line of Maureen from California. Please proceed.

Maureen:

My question is I have a feeling – my son was diagnosed at age 10, and when he was very young, with a lot of sinus infections, his pediatrician put him on a broad course of antibiotics for three months. And number one in my mind, I almost think that may have triggered his Crohn's because it wiped out the beneficial bacteria in the intestine. And is there any way now or is there any research being done to put together the beneficial bacteria and back in with the intestines in the right proportions?

Dr. Braun:

That is the purpose of the current CCFA bacteria initiative, the microbiome initiative. The challenge right now is that there's thousands of different bacteria to choose from and we're pretty certain from our studies that bacteria that are good for one person with one sort of genetic form of IBD will be bad for another person. So we're doing the work right now to find out what's the match between certain bacteria and certain genetics. And that'll take a few years to do. But once we have that, I think very quickly we'll be able to create the toolkit, the test, to use to do that monitoring and make the recommendations. But we don't have the information today to do that. It's going to take a few years. But that's the number one priority of the CCFA, on the basic research side to get that answer.

Kimberly Frederick:

Okay, this question is from the web by Janet. "How important is it to determine if you have Crohn's or colitis? My daughter can not be identified."

Dr. Braun:

Right. Well, it is important because as a group, patients with ulcerative colitis respond to different drugs than patients with Crohn's disease. However, we do know that there are some patients that have an overlap form of the disease, probably because there's that group that have genes which are affecting both forms, so they get something that looks in the middle. And so there are some people that have what's called indeterminate colitis and for those individuals, there are certain recommendations about how to approach treatment. So that doesn't mean necessarily that your doctor doesn't know. It might actually be the answer. But that's something that you should discuss carefully with your gastroenterologist, make sure that if they would like to get a second opinion, just to make sure that there's been a definitive answer about that. And if it turns out to be indeterminate colitis, there is a strategy to treat people with that form of the disease.

Kimberly Frederick:

Okay, and we'll take a question from the telephone audience.

Operator:

Your next question comes from the line of Nancy from Michigan. Please proceed.

Nancy:

I have two grandsons and one daughter with Crohn's disease. And the one grandson is very severe with it and he keeps adding things on like fistulas and latero necrosis and we are having so much trouble finding somebody that has the most information. They said go to the University of Chicago. They've already been to the one in Ohio. They're thinking about Mayo. Is this what you recommend or what?

Dr. Braun:

It sounds like your family member has a severe form of Crohn's disease. And the good news is that there's many choices of drugs or combinations of them to treat. But it might be only certain of them which will be beneficial. So it takes a real expert, particularly when it's severe, it takes a real expert to work through the different treatments to find the right one and also to keep your family member in the best possible health while you're getting to the optimal treatment. So if you have an expert locally who can do that, that's great. If not, there are a number of centers around the country that have a great deal of expertise and they would be appropriate to go to for a consultation, and then to work together with your local clinicians to have an ongoing plan of care.

Kimberly Frederick:

Okay, we'll take a web question from Donna. "How does a Crohn's patient become part of a clinical trial?"

Dr. Braun:

There are two ways, or maybe three ways to do it. One of them is to talk to your doctor and say that you are interested in doing that because your doctor might be participating in a network of clinicians involved with care. Second is to go on a site called clinicaltrials.gov, so it's

just those words smushed together, clinicaltrials.gov. And that is a listing of all of the clinical trials and it's a simple website to work through and you could find trials which are open for your disease and that are enrolling patients near to where you live, so that's a second place. And a third is that the CCFA has information about trials. I would probably recommend the first and the third. clinicaltrials.gov, I checked on it, I think it had about 400 trials going on, so that's a lot of work to read through them all. But talking to your doctor and going to the CCFA website are probably two really effective ways to find out ones that are ongoing, that might be of interest to you.

Kimberly Frederick:

Great. Thanks, everyone, for all of your great questions. If you weren't able to get your questions answered, please contact our Information Resource Center at 888-694-8872. Thank you so much, Dr. Braun, for your time and expertise. We truly appreciate you being here with us today and for all of your work on behalf of patients with Crohn's disease. Also a special thank you again to Centocor Ortho Biotech for making today's program possible.

We know it's always helpful to speak with people who understand what you're going through and CCFA has wonderful support groups for this type of forum. You can go to our website at www.ccfa.org to find out where the local support group is in your area as well as to connect with others on our IBD community, which is at ccfacommunity.org. And most importantly, on behalf of the Crohn's and Colitis Foundation of America, we really hope that you enjoyed today's program.

Have a great day, everyone. Thank you.

Operator:

Ladies and gentlemen, thank you for your participation in today's conference. This concludes the presentation. You may now disconnect. Have a great day.

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