Featured Cases: Modifiers of Cystic Fibrosis Disease

At the conclusion of this activity, participants will demonstrate the ability to:

- Describe the factors that may contribute to differences in severity of CF,
- Identify environmental modifiers that can be manipulated to alter outcome in CF, and,
- Recognize when and how genetic testing for CFTR and for modifier genes may be best used in patient management.

This audio activity has been developed for clinicians caring for patients with issues related to cystic fibrosis. You can also read the companion newsletter. In this edition Drs. Cutting and Collaco will help expand our understanding of the use of recently identified modifiers of CF disease, and the ramifications for future clinical management and therapies for the treatment of cystic fibrosis, with the discussion of some typical case scenarios.

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MR. BOB BUSKER: Welcome to this eCysticFibrosis Review podcast. eCysticFibrosis Review is presented by the Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing. This program is supported by an educational grant from Abbott Laboratories, Gilead Sciences Medical Affairs, and Vertex Pharmaceuticals.

Today’s program is a companion activity to the December 2011 eCysticFibrosis Review newsletter topic: Modifiers of Cystic Fibrosis Disease. Our guests today are Doctors Michael Collaco and Garry Cutting, from The Johns Hopkins University School of Medicine.

This activity has been developed for physicians, nurses, respiratory therapists, dieticians, and physical therapists caring for patients with cystic fibrosis.

There are no fees or prerequisites for this activity. The Accreditation and Credit Designation Statements can be found at the end of this podcast. For additional information about accreditation, Hopkins policies, expiration dates, and to take the post-test to receive credit on-line, please go to our website newsletter archive — www.ecysticfibrosisreview.org — and click on the January 2012 podcast link.

Learning objectives for this audio program are, that after participating in this activity, the participant will demonstrate the ability to:

- Describe the factors that may contribute to differences in severity of CF,
- Identify environmental modifiers that can be manipulated to alter outcome in CF, and,
- Recognize when and how genetic testing for CFTR and for modifier genes may be best used in patient management.

I'm BOB BUSKER, managing editor of eCysticFibrosis Review. On the line we have with us our December newsletter authors — Doctor Gary Cutting is a Professor of Pediatrics and Medicine at the Institute of Genetic Medicine at the Johns Hopkins School of Medicine. Dr. Cutting, welcome to the program.

DR. GARRY CUTTING: Well thanks, Bob, I’m delighted to be here to do the podcast today.

MR. BUSKER: Also on the line is Doctor Michael Collaco, Assistant Professor of Pediatrics at the Eudowood Division of Pediatric Respiratory Sciences, also at Johns Hopkins. Thank you for joining us, Dr. Collaco.

DR. MICHAEL COLLACO: Delighted to be here.

MR. BUSKER: Doctors Cutting and Collaco have disclosed that neither has a financial interest or relationship with a commercial entity whose products or services are relevant to the content of their presentation. They have also indicated that their presentation today will not include references to unlabeled or unapproved uses of any drugs or products.

Dr. Cutting and Dr. Collaco — in your newsletter issue, you reviewed some of the most current research into cystic fibrosis disease manifestations that are not directly related to the CFTR gene. Today I’d like to expand on that information via a case scenario format. So if you would, Dr. Cutting — start us out with a presentation.

DR. CUTTING: Sure, so let’s give a scenario of actually two children with cystic fibrosis. We’re going to talk about the care of dizygous, this is not identical, but dizygous twins who are 16 years of age. Both have CF and they carry the common mutation, delta-F508 in each of their CFTR genes. So they have this genotype F508, F508 and they are homozygous for that mutation.

Now they’ve come to your clinic and what’s intriguing about these patients is that one has an FEV1 percent predicted of 60 percent, while her sister has an FEV1 percent predicted of 85 percent.

MR. BUSKER: You’ve described a substantial difference in lung function between these two twins. What factors might be responsible for that?

DR. CUTTING: So even in patients with the exact same mutations in CFTR, we call them identical CFTR genotypes, there could still be quite a bit of difference in their lung function. We know this from years back when the gene for cystic fibrosis, CFTR, was first identified, and people discovered, researchers discovered that there was a common mutation, the
one we just mentioned, the delta-F508, and they looked at patients who are F508 and even though these patients all carried the same mutation, there was a very wide range in these patients of their lung function measures.

So although having a mutation in CFTR causes the disease, it doesn’t generally accurately predict the severity of your lung disease. Now what other factors contribute to determining the severity of your lung disease.

Well studies have been performed actually by Dr. Colasso who is on the line with us today, looking at both identical and non-identical twins, and studying them when they live together in the same household and then when they moved away from the home and moved into different environments, he was able to, using that information, deduce that about half of the variation you see in lung function can be attributed to genes, and these are genes other than CFTR, so we call those genes modifier genes, and the remaining fraction, which is about half or 50 percent, is due to differences in their environmental exposures.

Now what was interesting in Mike’s work was that unique exposures are actually a major portion of that environmental effect, so these would be exposed so that just one of the two twins would experience. So it is a combination, these two 16 year old ladies who both have CF, even though at 16 I’m going to assume they’re still living at the same house, going to the same doctor, same clinic, probably getting very much the same treatment, and then they have the same CFTR mutations, they are clearly going to experience differences in individual environment. It may be one of them is a cheerleader or plays sports, the other one may be more into reading, for example, maybe one is more compliant with medication, there could be lots of differences in the environment, but also, even though they are twins, they share half of their genes, the variants and the other modifier genes, but just because they share half, there is another half they don’t share. So more than likely some of the differences in lung function is also attributable to genes.

So again, to review, the study that Dr. Colasso did showed that half the variation in lung function could be due to environmental effects, so certainly things that they individually experience would be important in this case, the other half would be due to differences in genes. Even though they are twins, there are still differences in their genes.

MR. BUSKER: Dr. Collaco — anything to add?

DR. COLLACO: The only other thing I would add to that is it’s still and evolving area of research, but there may be epigenetic differences between the two twins, specifically modifications to the DNA that occur either in utero or during early childhood, even as a young adult, that may be leading to differences in the way the genes are transcribed, resulting in different protein levels and thus, perhaps slightly different phenotypes.

DR. CUTTING: Yeah, I agree, this is a key area of research, epigenetic effects, that we’re just starting to scratch the surface on how they cause differences between related individuals, even differences amongst co-identical or monozygous twins, so that’s a good point, Mike.

What do you think about individual experiences, other kinds beyond, say, the standard environmental ones that I mentioned, what about infection and things like that, or viral infection, do you think they could differently affect a pair of twins living in the same household?

DR. COLLACO: Oh, most certainly. I think one of the things that we’ve learned over the last decade or so is that, for example, respiratory syncytial viruses early in infancy can lead to the development of asthma during early childhood. And so one could surmise, perhaps, that one twin had a significant infection very early on in life with a virus or a pneumonia leading to different lung function later in life.

DR. CUTTING: Yeah, I agree, that’s a real possibility and it’s a challenge I guess for the doc to start thinking about how to dissect this, these differences out, and to sort out why there may be differences. But I think it can be done.

DR. COLLACO: I agree. End.

MR. BUSKER: I’d like to get your thoughts on the most appropriate management approach to these twins. Dr. Collaco?

DR. COLLACO: The first thing probably is to get a comprehensive history from the family to identify any
environmental factors or past medical events like we’ve eluded to, that may be different between the twins, and as Gary has mentioned, looking at adherence is certainly a part of that.

There should probably be careful review of cultures to identify whether these twins have been infected with different organizations that can lead to differences in lung function. And then at least in terms of management, certainly employing best practices as outlined by consensus guidelines of the CF Foundation is paramount in their care moving forward.

DR. CUTTING: I was going to add something, Mike, just to get your thoughts. So some of these points that you made about environmental exposures and so forth are things that would have happened in the past, and we can’t do much about at this point. But if the doc was seeing these patients in his or her clinic today, there are things that we could think about that you might advise them as far as what they may be able to modify in their environment or change in their environment that might improve outcome?

DR. COLLACO: Yes, certainly things like secondhand smoke exposure may be modifiable, maybe encouraging exercise and/or adherence with therapies for a twin who is not necessarily adherent with therapies.

DR. CUTTING: So ferreting out if one twin is actually taking her medicines or taking a different dose of even enzymes might actually be able to give you some clues as to ways to manage them in a similar way so that you have optimal outcome.

I guess the end goal would be to have both of those siblings at least attain the 80 percent predicted, but I guess one would be worried about an individual patient with CF at 16 years of age with an FEV1 of 60 percent predicted, right?

DR. COLLACO: Yes, definitely. One of the other interesting studies that I’ve seen recently is the use of home visits in the United Kingdom for patients with severe asthma. And what they’ve identified is a substantial fraction of those patients don’t necessarily have severe or difficulty with the control of asthma, but are having difficulty maintaining adherence or compliance with prescribed therapies. So I think that’s certainly a part of assessing for the reasons for difference in lung function.

DR. CUTTING: So perhaps we should talk a little bit more and maybe in the next case to environmental factors that a doctor or clinician could consider modifying for improving a patient’s outcome.

MR. BUSKER: Dr. Cutting, thank you for making that transition for us. So if you would, Dr. Collaco, present us with another scenario, please.

DR. COLLACO: Okay, I’d be glad to. For case two, the parents of a ten year old boy who has an F508del/G551D CFTR genotype and an FEV1 percent predicted of 90 percent, asks you what environmental changes they could make at home to maximize their son’s lung function.

MR. BUSKER: Let me start out by echoing that question and ask you what interventions you would suggest to these parents.

DR. COLLACO: Well I think to begin with a number of environmental factors have been associated with lower lung function in cystic fibrosis. Over the past several decades the best replicated factors or the factors that have been seen in multiple studies are socioeconomic ones. And these include things such as insurance type, private versus public insurance, parental occupation, and household income levels.

However, you know, for most families, these factors are not amenable to any substantial change. And it’s not entirely clear how these socioeconomic factors lead to the lung pathophysiology or changes in lung function that we see, whether they reflect access to care, or medications or something else entirely.

Probably more pertinent to our discussion is the patient adherence and perhaps variation in individual provider practices that play a role in outcome. And it’s unclear as of yet how much the variation in lung function or how much of low lung function can be attributed to either patient adherence or variation in provider practices, but it probably is substantial.

So certainly we would recommend to the family adherence with the recommended therapies and also being regularly seen at an accredited CF care center or affiliated center.

Another environmental factor, which certainly has been associated with lower lung function in cystic fibrosis, as well as other respiratory diseases, is secondhand smoke exposure. Previous work that
we’ve done, we would estimate that secondhand exposure could result in two years decreased longevity or survival with the exposure of secondhand smoke in the home. So certainly if there were any family members who smoked in this patient’s home we would counsel them to quit smoking.

And then lastly, other considerations revolve around the consensus guidelines for eradication of *Pseudomonas aeruginosa* and *Burkholderia cepacia* when first detected in respiratory cultures, as well as meaning optimal nutrition. Is there anything else you’d add, Gary?

DR. CUTTING: Well, Mike, we’ve had these questions before and people thinking about patients with cystic fibrosis, obviously disease associated with chronic lung deterioration and do parents or other people really smoke still around these patients given the public announcements from many sources about the dangers of not only firsthand smoke, but secondhand smoke. But, Mike, did you want to just at least mention the percent of households self identified that they had someone smoking in the household and the kind of effect that you saw if someone did smoke, what was the kind of drops in FEV1 that you saw in your study that you published in the *Journal of the American Medical Association*?

DR. COLLACO: That’s a good question. We saw drops in lung function ranging from about 5 to 10 percent predicted, just with smoke exposure, and that’s after correcting for age, gender and relevant demographic. So it’s not an insubstantial effect on lung function or with secondhand smoke exposure.

DR. CUTTING: And if I recall rightly it was something like 23 percent of households with at least two children with CF, not just one, but two children with CF, self reported that there was someone smoking in the house. Is my memory correct there, Mike?

DR. COLLACO: It is correct, and as you alluded to, I’m not sure we know exactly what the behavior of family members who smoke is, whether they smoke inside, outside, how much they smoke and how much secondhand smoke the individual with cystic fibrosis is actually exposed to.

DR. CUTTING: But just the report of secondhand smoking by at least one member in the household, even after making all the other corrections that you had mentioned, were still associated with a 5 to 10 percent drop in lung function, which that is a pretty sizable shift that we’d be very happy if we could get a drug to do something like that.

So I guess Mike and I are spending some time here discussing this because this is an alterable behavior, although we understand the difficulty underlying smoking and so forth, but encouraging clinicians to work as hard as they can to decrease the exposure of children with chronic lung disease like CF to secondhand smoke, is something that might give you pretty immediate and positive response in outcome for your patients.

Mike, I hope I’m not overemphasizing that point, you being the pulmonologist and me being the geneticist?

DR. COLLACO: Oh, no, but I think it is certainly an environmental factor that’s modifiable and that could have substantial benefits on lung function for the 20-some percent of patients who are exposed to secondhand smoke, also potentially resulting in an increased survival of perhaps two years.

DR. CUTTING: You brought up the infection issues and infection control. That’s something that I guess is being done at the center level and nationally to eradicate *Pseudomonas* when it appears, are there any practices in the environment that you could advise so we could think of telling this family to decrease the chance that their son might get *Pseudomonas*? He’s 10 years old now, let’s say he hadn’t yet been infected, what kind of things could we suggest to them about avoiding *Pseudomonas* perhaps?

DR. COLLACO: Unfortunately *Pseudomonas* is one of those ubiquitous organisms in the environment. I do think there has certainly been enough anecdotal as well as published data demonstrating that when patients with cystic fibrosis are in close proximity to one another there is certainly an increased risk of transmission of an infection. And at least in the United States there’s been a decreased utilization of cystic fibrosis camps and things like that where patients are in close contact.

DR. CUTTING: Contact with others who have Pseudomonas, which is the standard in many places now for individuals who are infected. But, Mike, you brought up an important point which I guess we
probably don’t need to remind the docs who might be listening, is that how parents may feel about, oh, my son or daughter got infected with *Pseudomonas*, somehow it’s my fault, this is a pathogen that’s out there and in the general community and it’s very hard to control. And I contrast that as compared to, say, smoking in the household which might be easier to eradicate as compared to the ubiquitous pathogen such as *Pseudomonas*.

So obviously one would like to remediate all of these environmental factors, but it sounds like, as you suggest, a careful family history, social history as well, would be critical in the management of a patient like this and telling the patients the best way to achieve a good outcome for the son, but also making sure that the advice you give to the parents is reasonable, otherwise we wouldn’t want a set of parents going home thinking that they’re going to have to scrub down the whole house, not let their child out any time, and prevent their child from having a pretty much normal life, which they should at this point if they’re doing well with their disease and so forth.

And so I think the issue of being reasonable about the recommendations, I just thought I’d temper your points, Mike, anything else you’d like to add to that?

**DR. COLLACO:** No, I would certainly agree though about not escalating parental anxiety in an untoward manner, but, you know, being realistic about what’s achievable.

**DR. CUTTING:** Yep, otherwise stressing the parents out is not going to – it’s going to be another environmental variable that is probably going to have more negative than positive consequences.

**MR. BUSKER:** What role might genetic testing play in this case?

**DR. CUTTING:** So genetic testing for this woman and perhaps for her sister is something you might want to consider. Studies from UNC, University of North Carolina, working with investigators up in Toronto who have been looking for genes that modify liver disease in CF, had an important paper out a few years ago in *JAMA, Journal of the American Medical Association*, in 2009. In that paper they demonstrated that a variant in a well known gene, the alpha-1-antitrypsin gene, the *ZED* allele, increased your risk of developing liver disease if you have cystic fibrosis. About 3 to 4 percent of people, that’s 3 in 100, carry that *ZED* allele in one copy, but in the case of patients with CF and liver disease, 11 to 12 percent of the patients had that *ZED* copy.

So from that information Mike Knolls, and Peter Durie and colleagues were able to deduce that there was a pretty big increase in risk associated with the presence of that *ZED allele*. So in cases like this, particularly when one might be considering the risk for the sister who currently doesn’t have liver disease, one might want to consider the testing for that alpha-1-antitrypsin *ZED allele*, that gene is also called serpin-A1, and that test is available because of the disease that alpha-1-antitrypsin causes when there are two copies of the *ZED allele*.

If you knew that information and you knew that the individual presented, the 25 year old woman, had the *ZED allele*, then the question would come up, well, maybe that is contributing to the CF related liver disease. The other question would be would that...
information be used to guide testing for the sister, and, in fact, in certain cases the diagnosis of liver disease can be tricky. I mentioned that imaging techniques need to be used, enzyme elevation alone are not enough to make the diagnosis of cirrhosis, so having some genetic information might guide how frequently you do those imaging tests, for example, on the sister who doesn’t have liver disease at this point.

But if you knew the older sister, the 25 year old, carried that ZED allele, and then you tested the younger sister and she just happened to also carry the ZED allele, then you might consider imaging and so forth at a more frequent basis to pick up the possibility that she may be developing cirrhosis, to catch it as early as possible.

Now there is the issue of autonomy, I must mention as a geneticist, of course you would have to ask the younger sister if she wanted that testing. She may or may not want to know her risk, that’s up to her, and so one would have to consider that the testing done for each individual, when you get into a family situation, even though one family member might have had the testing, might have come up with a positive result, other families members, siblings, for example, may feel differently about the information and having the testing done.

So that’s an issue to at least consider as you go to offering the test to the sister, to not jump in and insist they have the test, but that to at least offer it as a possibility to help in her management.

Mike, do you see cases of CF-related liver disease that often? It tends to be that sometimes this condition starts in childhood, but we’re talking about two adult patients here, are there other things I might have missed or should be considered?

DR. COLLACO: I think liver disease is less common in the pediatric population which I take care of, but certainly this is a very interesting case in that it gets at the idea of predicting future risk from a genotype. And I think perhaps also counseling the family that just because the younger sister may have the risk allele doesn’t necessarily mean that she will develop liver disease. And conversely, if she doesn’t have any risk allele, it does not necessarily mean that she is completely protected. Because I think the study done by Dr. Knolls and his colleagues also found patients who had the risk allele who didn’t have liver disease, as well as patients who didn’t have the risk allele who certainly had severe liver disease.

DR. CUTTING: Great points, Mike, important to recognize that the situation where mutations, and these are CF causing mutations in the CFTR gene, are what we call high penetrant genetics, are very, very likely to cause CF. In the case of modifier genes, they are altering risk. And as Mike very elegantly pointed out, you can carry the risk allele but it doesn’t mean it’s null or none, it just changes your risks, and in this case I think it’s a three-fold increase in risk.

So one has to use the information and remember it’s predictive and not definitive in the same way that a highly penetrant mutation such as those we see in CFTR, the story is somewhat different. So having the mutation will change your risk profile, not having a mutation, well you still have a sister, she still has a sister who had liver disease, and it is possible that there are other modifier genes contributing to trait. Or there might be environmental effects that are occurring, and maybe those environmental effects were unique to the older sister and will not have occurred to the younger sister.

So again, the genetic information when we use it for modification of disease, is used as a guide, how to monitor the patient and potentially treat the patient in the future.

The one other point I’d like to bring up with my hat on as a geneticist, is if this young lady were to be found, the 25 year old, to carry the alpha-1-AT gene, one might want to test both the parents to first verify that one of the parents carries this same ZED allele, as would be expected, but also to exclude the possibility the other parent is also a carrier for the ZED allele. Because then they have a different risk, and that is the risk is passing on the ZED allele, each of them passing on having a child with liver disease or potentially lung disease due to being homozygous for the ZED allele. That’s a small chance but it’s just something that if you were to consult a medical geneticist they would potentially suggest to you to fully work up the family.

That also would help you in appraising the risk for the sister. The risk would be quite different if both parents just happened to carry the ZED allele as opposed to the more likely scenario that one of the parents carries the ZED allele. And then that means there is a 50/50 chance that if one sister carries the
**ZED allele**, the other sister would also carry the **ZED allele**.

**DR. COLLACO:** Yeah, and I think as one last minor side point, you mentioned, you know, the risk of perhaps lung disease in addition to liver disease with the **ZED allele** is that at least in cystic fibrosis the role of the **ZED allele** as a modifier of lung function has not been fully confirmed or replicated at this point. So even if either sister had the **ZED allele**, at least at this point I would still counsel the family that we don’t know how that might impact or not impact on lung function.

**DR. CUTTING:** Great point, Mike. The fact that is pointed out by Mike is the theme we’re seeing over and over again in modifier studies, the changes in these modifier genes can affect one part of the phenotype, yet may not affect another part of the phenotype. In this case we’re talking about the **ZED allele** affecting the risk for liver disease, and yet evidence so far accumulated, it appears that the **ZED allele** is not confounding or complicating, or worsening the lung disease in patients with CF. So that term is called pleiotropy or pleiotropic effect.

**MR. BUSKER:** Thank you both for that very interesting discussion. I think we’ve got time for one more scenario, so Dr. Collaco, present a patient for us if you would, please.

**DR. COLLACO:** So at this point we have identified several different loci, including some polymorphisms in a variety of genes that have been shown to impact outcomes in lung function, diabetes, and liver disease, but it may not be that these particular loci and polymorphisms are tested for on the particular panel that he’s considering having obtained. And it is also a possibility that this genetic sequencing may reveal risk for diseases not associated with cystic fibrosis, you know, such as Alzheimer’s, which the patient may not necessarily wish to know about his future risk for.

**MR. BUSKER:** And from your perspective, Dr. Cutting?

**DR. CUTTING:** Well I think that point you made was excellent, that many times we do testing because we are looking for a specific change. If we’re going to order a blood gas, we might be looking for the oxygen saturation. You can do a genetic test and you have to ask yourself what exactly are you looking for. In this kind of case, when you do a sequence of the entire genome, in particularly if you do a sequence, Mike, and look at every single variant, then you’re scanning, you’re searching for changes.

And I have to say, the current state of the technology and our knowledge will yield changes where we won’t know exactly what the effect of these changes are at this point. In other words, the technology has run far ahead of actually our understanding of these changes in the genome. So in that case, shining the light where you don’t know how to interpret what you’re seeing may leave you in a bit of a tricky position. And this is at least as a geneticist how we counsel individuals who come to us.

Now, of course, these service are available, they’re available to the public and people have actually used them, and they on occasion bring them in to the genetics clinic, for example. And I would not be surprised in the near future if some of the doctors and other medical specialists listening to this podcast, may be faced with the same issue that someone walks in and says, well, I got a Christmas present, so and so paid for me to get my genome sequence to see if I could find all the modifiers that might predict how severe my disease is going to be. And then you are faced with the situation of lots of variants will be listed and trying to interpret which ones are going to predict things, as Mike mentioned, liver disease, diabetes, severe or less severe lung disease.

So in those kinds of situations you may want to seek the help of your local geneticist, but at the same time I think an excellent starting point would be to focus in on exactly the conditions and issues that the patient has, themselves. If they have liver disease, maybe you can focus on just the information about the alpha-1-antitrypsin that we talked about. If they have very progressive, early onset severe lung disease, maybe you might want to take a look at some of the loci that have been associated with more severe lung disease, such as the **TGF-beta-1** gene. If you don’t feel comfortable doing them, then consulting with your geneticist or genetic counselor may help you in conveying that information.

It would be perfectly understandable though if you told your patient, well, that is still not really ready for prime time all that information, we’re still learning about how these modifiers influence disease, the mechanism by which they do it and so forth, and perhaps one should put that away for a while with
the idea you are not going to forget it, but tell the patient we might be able to go back to that in a few years as our understanding of these variants increases.

Now there is another issue that might come up regarding this information and how it might be used by insurers and other people that would want to know about genetic information. But I mentioned that this type of information, genetic information, is now protected by an act called GINA, this is the Genetic Information Nondiscrimination Act, which was passed by the congress in 2008. Now this act prevents health insurers from denying coverage based on genetic information. It’s very important to pass because there have been cases where this information, say finding out about an unfavorable modifier for CF, and if the insurer were able to find that out, perhaps that might influence whether they would provide coverage of certain types.

Now this may all change in the future as we move into new health care systems, but either way to let you know that law is there to protect that patient. So looking at the information, referring them to a geneticist to ask more about what’s in that genome sequence, will not compromise your patient for insurance status.

Mike, did I cover most of the points or anything else?

DR. COLLACO: A couple more things, it’s important to recognize that GINA, as passed by Congress, while it does prevent health insurers from denying coverage based on genetic testing results, the legislation does not apply to life insurance, disability insurance or long-term care insurance. Important things for the patient to consider if he already has these things or is thinking about applying for them in the near future.

The other thing is that, I certainly agree with you, Gary, that we don’t know exactly what variants in the genome may or may not represent in terms of future risk. And it’s certainly possible that, you know, it may not be so much the specific variant in the genome that leads to the risk, but the specific variant in the genome plus an environmental exposure. So a gene and environment interaction that leads to the risk.

And it may be that just ameliorating or changing the environmental risk reduces whatever risk was associated with that genetic variant in the first place.

DR. CUTTING: Mike, you’ve done a very nice study that you published on that, do you want to just give for the listeners an example of how these interactions can occur?

DR. COLLACO: Yeah. We did a study in cystic fibrosis looking at secondhand smoke exposure and as we mentioned previously, secondhand smoke exposure results in a decrease in lung function.

We also looked at secondhand smoke exposure as it relates to specific polymorphisms or gene variants within an inflammatory gene known as TGF-beta. And within that gene we found that patients with a specific variant or risk allele with the combination of secondhand smoke exposure, had a much more dramatic drop in lung function than if they didn’t have the risk allele.

So, for example, if they did not have the risk allele, when exposed to secondhand smoke they had a decline in lung function of 5 to 10 percent, but with this risk allele, they had a lung function drop as much as 15 to 20 percent. So a substantial difference with the same environmental exposure. And correspondingly, if they did not have any secondhand smoke exposure, the lung function was the same across the genetic variants.

So that is just one example of a gene environment interaction. And as we do more studies and as time progresses, I think more of these interactions will be found.

DR. CUTTING: So the whole genome sequencing may, indeed, yield useful information, but right now to return to a point I made earlier, great technology, this information will be we think at some point in the future useful, and at this point there are some elements valuable, but much of it right now is not yet interpretable.

So again, it could be useful information and not to indicate to your patient that there is nothing to be gained from doing this, but at the same time making them aware that, in fact, it is only going to be of limited usefulness at this point in time.

MR. BUSKER: I want to thank you both — Dr. Gary Cutting from the Johns Hopkins Institute of Genetic Medicine, and Dr. Mike Colasso, from the Johns Hopkins Eudowood Division of Pediatric Respiratory
Dr. Cutting: Well thanks very much, I really enjoyed doing this session.

Dr. Collacco: Thanks, Bob, it was a real pleasure.

Mr. Busker: This podcast is presented in conjunction with eCystic Fibrosis Review, a peer-reviewed CME and CNE-accredited literature review emailed monthly to clinicians treating patients with cystic fibrosis.

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