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eLITERATURE REVIEW
eCysticFibrosis Review
Podcast Issue

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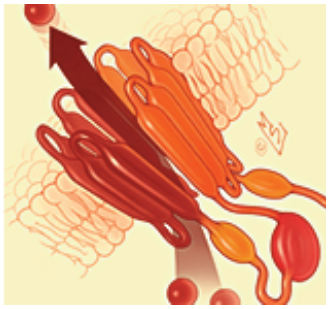


VOLUME 4 — ISSUE 12: TRANSCRIPT

Featured Cases: What Does CFTR Tell Us About Lung Disease?

Our guest today is Dr. Patrick Sosnay, the Johns Hopkins University School of Medicine.

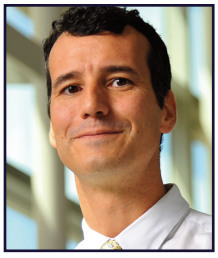
After participating in this activity, the participant will demonstrate the ability to:

- Recognize that ivacaftor is a new therapy for CF patients specifically with the G551D mutation that corrects the CFTR protein and results in improved lung function
- Describe what's known about how CFTR genotype influences lung function
- Describe the use of CFTR genotype to facilitate making diagnoses of cystic fibrosis, predicting prognoses, and selecting therapies

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to CFTR in the format of case-study scenarios for the clinical practice. This program is a follow up to Volume 4, Issue 11 *eCysticFibrosis Review Newsletter* – What Does CFTR Tell Us About Lung Disease?

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

MEET THE AUTHOR



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Guest Faculty Disclosure

Dr. Sosnay has indicated that he does not have any relevant financial interests or relationships with any commercial entities.

Unlabeled/Unapproved Uses

Dr. Sosnay indicated that his discussion will not refer to unlabeled or unapproved uses of drugs or products.

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April 8, 2014

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April 7, 2016

CME/CE INFORMATION

⇩ PROGRAM BEGINS BELOW

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LAUNCH DATE
This program launched on February 28, 2013, and is published monthly; activities expire two years from the date of publication.

INTENDED AUDIENCE
This activity has been developed for pulmonologists, pediatric pulmonologists, gastroenterologists, pediatricians, infectious disease specialists, respiratory therapists, dieticians, nutritionists, nurses, and physical therapists.

STATEMENT OF NEED
Based on a review of the current literature, including national and regional measures, detailed conversations with expert educators at Johns Hopkins, and a survey of potential program participants, this program will address the following core patient care gaps:

Disease-Modifying Therapies
- Clinicians may be unfamiliar with recently introduced disease-modifying therapies and how they are altering the therapeutic landscape for patients with cystic fibrosis.
- Clinicians may be uncertain how to integrate genotyping into therapeutic decisions and how to communicate with patients and families about the relationship between genotype and therapy

Nutrition
- Many clinicians lack strategies to persuade patients to adhere to CF nutritional requirements, resulting in low body weight and nutritional failure in patients with cystic fibrosis.
- Many clinicians remain uncertain how to optimize pancreatic function in patients with cystic fibrosis.

Treating CF Patients with Inhaled Antibiotics
- Clinicians lack knowledge about the use of existing and emerging inhaled ABX to treat chronic pulmonary infections.
- Clinicians need more information to make informed decisions about the use of inhaled ABX in combination.
- Clinicians lack information about best practices for scheduling ABX therapy to suppress chronic airway infections.
- Common clinician assumptions about treating pulmonary exacerbations lack supporting evidence.
- CF clinicians are not aware of and/or are not actively advocating inhaled ABX patient-adherence strategies.

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HARDWARE & SOFTWARE REQUIREMENTS
PC: Internet Explorer (v6 or greater), or Firefox
MAC: Safari

MR. BOB BUSKER: Welcome to this *e*CysticFibrosis Review podcast.

*e*CysticFibrosis Review is presented by The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing. This program is supported by educational grants from Aptalis Pharma, Inc; Gilead Sciences Inc., and Vertex Pharmaceuticals.

Today's program is a companion piece to our eCysticFibrosis Review newsletter issue: *What Does CFTR Tell Us About Lung Disease?*

Our guest today is that issue's author, Dr. Patrick Sosnay, from the Johns Hopkins University School of Medicine.

This activity has been developed for pulmonologists, pediatric pulmonologists, gastroenterologists, pediatricians, infectious disease specialists, respiratory therapists, dietitians, nutritionists, pharmacists, nurses and nurse practitioners, physical therapists, and others involved in the care of 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 and expiration dates, and to take the posttest to receive credit online, please go to our website newsletter archive: www.eCysticFibrosisReview.org, and click the Volume 4, Issue 12 podcast link.

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

- Recognize that ivacaftor is a new therapy for CF patients specifically with the G551D mutation that corrects the CFTR protein and results in improved lung function
- Describe what's known about how CFTR genotype influences lung function
- Describe the use of CFTR genotype to facilitate making diagnoses of cystic fibrosis, predicting prognoses, and selecting therapies

I'm Bob Busker, managing editor of eCysticFibrosis Review. On the line we have with us Dr. Patrick Sosnay, Assistant Professor of Medicine of the Division of Pulmonary & Critical Care Medicine at the McKusick-Nathans Institute for Genetic Medicine and the Johns Hopkins Cystic Fibrosis Center at The Johns Hopkins University.

Dr. Sosnay has indicated that he does not have any relevant financial interests or relationships with any commercial entities and his discussion today will not refer to the unlabeled or unapproved uses of drugs or products.

Dr. Sosnay, thank you for joining us today for this eCysticFibrosis Review Podcast.

DR. SOSNAY: Thanks, Bob. I'm happy to be here and hopefully this will be an informative session for our listeners.

MR. BUSKER: Our topic is: "What Does CFTR Tell Us About Lung Disease?" In last month's newsletter issue, you reviewed the relevant literature describing how advances in understanding the CFTR gene have been related to improvement in lung function. Today I'd like to discuss how some of that new information can be translated into clinical practice. So please start us out with a patient description.

DR. SOSNAY: Our first patient is a 13 year old girl who has a diagnosis of cystic fibrosis, but she has an unknown genotype. She may have never been genotyped or it might not be available. She and her family heard some good news about new CF drugs and they were curious to see if she might be a candidate for these new drugs. She has reasonably good lung function with an FEV1 at 90 percent predicted, although she has had a couple of severe pulmonary exacerbations, including one last winter that required her to be hospitalized for administration of IV antibiotic.

MR. BUSKER: So you don't have the genotype, her lung function generally isn't too bad but she's had some severe exacerbations. Would you consider her a candidate for ivacaftor? And my question here goes to, what information should the clinician get before making that decision?

DR. SOSNAY: Well, Bob, she might be a candidate for the drug, but she needs to undergo genetic testing so we know for sure. Genetic testing is available commercially through both academic and for profit

labs, and the type of genetic testing done could very easily tell if she carries at least one of the G551D mutations that ivacaftor has been shown to be effective against.

If her cystic fibrosis was recently diagnosed, she might have had CF genetic testing, but the CF genetic testing did not pick up the mutation G551D. If she was tested recently, it's unlikely that she has that mutation. But if she has never been genotyped or if she were genotyped quite some time ago, it's possible that she wasn't tested for G551D.

Given that she is 13 years old, the chances are probably that she has been genotyped at some point, but those records should be obtained if possible. If she hasn't been genotyped, there are services both in the United States and in Europe that would cover the cost of genotyping. Through the US Cystic Fibrosis Foundation, the cost of genotyping can be covered so the patients don't have to pay any out of pocket costs for that.

MR. BUSKER: So let's take the next step. She's genotyped, and the genotype comes back, she has one copy of G551D.

DR. SOSNAY: She will be a great candidate for the drug. It's a very expensive drug so we'll need to work with insurance or work with your CF clinic to try to pay for it. The drug company has programs for patients who have high out-of-pocket costs because of their insurance or because they're not insured, so work with your CF center or social worker to try to get it. But she carries the mutation, so she would be a candidate for the drug.

Now once she starts on the drug she might feel better but it's possible that she might begin to feel a little bit worse. Some patients who took the drug in the Ramsey trial that was mentioned in the newsletter, experienced some cough, some runny nose, even some shortness of breath. These are all symptoms that are typical with cystic fibrosis but sometimes patients who were taking the drug experience the symptoms, as well.

We don't know if a drug is going to be successful right away. Some patients feel better as soon as they start taking it, but for the most part, patients notice the effect of the drug over time. And at this time we have to recommend that she continue all of her other medications, her airway clearance, inhaled antibiotics, any other medications to help maintain her cystic fibrosis, like pancreatic enzymes.

Now she's a pediatric patient so she is more like the second paper that was presented in the newsletter, the one that was done in *Pediatrics*. The results are similar though and both encouraging, and both pediatric patients and adult patients should have a good response to the drug.

MR. BUSKER: Different scenario. She's genotyped, but her genotype does not contain a G551D.

DR. SOSNAY: At this time she is not eligible for any FDA approved drugs, and we even don't know if the drug would help. This is a situation where I would strongly encourage the patient and her family to talk to her CF provider about potentially enrolling in a research study, because other genotypes and other therapies are being investigated, but nothing is available through the FDA at this point.

MR. BUSKER: You said that once she starts on ivacaftor, she might feel a little bit worse. Cough, runny nose, maybe some shortness of breath. What are the specific side effects of this agent that clinicians should be aware of?

DR. SOSNAY: This is a new drug, so we don't have a good idea of what the long-term side effects are going to be. She'll need some maintenance labs, particularly some maintenance blood tests that will check her liver function. There was some evidence in the pre-approval clinical trials that there might be a slight increase in liver function tests. Encouragingly, since the drug has been approved, we haven't seen much elevation in the liver function tests, so it appears that those were just anomalies.

She will also have to have her sweat chloride concentration checked again and potentially nasal potential difference. This would be a sign that the drug is working. The side effects that we're seeing with the drug are pretty common side effects that we see with all drugs, including rash, abdominal pain, nausea, diarrhea, and the encouraging thing is that all of these side effects occurred just as commonly in patients taking placebo as in those taking the drug. That's good evidence that the drug is probably safe, although once again, reemphasizing the point, because it's a new drug we just don't know and the patient needs to be monitored, of course.

MR. BUSKER: Summarize this patient for us, please. What are the key things the CF clinician needs to know?

DR. SOSNAY: In this patient where we don't know the genotype, the first step is to find out what *CFTR* mutations she carries. If she carries at least one copy of the G551D mutation, then she's eligible for a new FDA and European Union approved therapy of ivacaftor. This ivacaftor drug works to repair the basic defect of the mutated CFTR.

This is a new drug, so we don't know the side effects of it, but encouragingly in clinical trials and after the drug has been approved, all the side effects seem pretty mild. But of course, she should communicate with her doctor who prescribed it.

MR. BUSKER: Thank you for that patient and that discussion, Dr. Sosnay. Please bring us another patient.

DR. SOSNAY: Our second patient is six weeks old whose CF was diagnosed by newborn screen. The genotype comes back with one copy of a mutation called R117H and one copy of a mutation that you might not have heard of at all. For the purpose of this discussion we're going to use the mutation E56K. If you haven't heard of that mutation, you're not alone; it's a pretty rare mutation. Other than that positive newborn screen, she is totally asymptomatic. She has not yet had a sweat test.

MR. BUSKER: In your newsletter issue, you reviewed papers on classifying CFTR disorders. Let me ask you to apply that here. How would you diagnose CF in this baby? Does she have cystic fibrosis? Or is it CF metabolic syndrome? Or CFTR related disease? Or even, does she have no disease at all? Talk to us about the diagnostic process.

DR. SOSNAY: The diagnostic process for cystic fibrosis remains a clinical diagnosis. Nothing that comes back on the genotyping test should make you say this patient has cystic fibrosis or doesn't have cystic fibrosis, if the clinical symptoms are pointing you one way or the other.

Now I'm a geneticist but I'm also a clinician, and if I see a patient in clinic who has clinical symptoms of cystic fibrosis, I treat them as if they have cystic fibrosis, regardless of what the genotype report shows. In the absence of two known CF-causing mutations, we need some other piece of evidence to say that the CFTR protein is not working. Usually we'll do a sweat test to show that the CFTR protein is not working, or we might do a test called a nasal potential difference, another slightly more invasive test that would tell us that the CFTR protein is not working. There's also a rectal biopsy that can be done experimentally, although it's not commonly done in clinical practice.

So this baby would likely fit the diagnosis of what we call CF metabolic syndrome. There's a possibility that cystic fibrosis would be diagnosed later in life. The diagnosis of CF metabolic syndrome was described in the Borowitz article referred to in the newsletter. The term "CF metabolic syndrome" is just a parking lot — it's for patients who have a positive newborn screen with some *CFTR* mutation, but not the kind of *CFTR* mutation that we know, oh, this is like delta-F508, or F508-del, or G551D where we know that they definitely cause cystic fibrosis.

MR. BUSKER: Now you described the genotyping of this baby's mutations as R117H and E56K. You're probably right in saying that E56K isn't too well known by the nongeneticists in our audience. So where should a clinician go to get information about E56K or another mutation that they might not know about?

DR. SOSNAY: Like most things these days, Bob, the first place to go is to the internet. Often people will just Google a mutation and they might find some information about it. But any time you Google anything you get sort of the good with the bad and everything comes back. So here's a couple of websites that might be particularly helpful and are particularly well validated.

The CFTR2 website (www.cftr2.org) is put together at Johns Hopkins by me and some colleagues, as well as an international team. It's designed for clinicians to tell exactly this. If they get a mutation on a patient, on a newborn screen or an adult with a difficult diagnosis, this is the resource to try to tell if this is a mutation that causes CF, doesn't cause CF, or is one of those gray area mutations that sometimes causes CF but sometimes doesn't.

The historical reference that's still in use today is the CF mutation database (www.genet.sickkids.on.ca/), and that's run out of the University of Toronto and

Sick Kids Hospital. That was started before even the internet as a newsletter that went out periodically. It was sort of a card catalog of all of the different CF mutations. That website is still in use but it describes all the mutations in the *CFTR* gene, not just the mutations that we know cause cystic fibrosis. CFTR2 is specific to the mutations that cause cystic fibrosis.

The CF mutation database and the CFTR2 are linked, so if you find a mutation in one you can go back and forth in the other.

Also, if you did a PubMed search and found a publication with patients that had that mutation, that might give you a clue of how severe that mutation is.

There is another database that's run through the National Institutes of Health and NCBI, it's called OMIM, or the Online Mendelian Inheritance in Man (www.omim.org), which has all different diseases, not just cystic fibrosis, and it includes a catalog of some of the mutations in CFTR, the gene that is mutated in CF that can cause disease.

A couple of the other resources that also are for all genetic disorders, not just cystic fibrosis, include dbSNP (www.ncbi.nlm.nih.gov/SNP/), which is a catalog of all the variants in our genetic code. So it's obviously much more suited to a scientist than to a clinician.

A database called ClinVar that's also run through the NCBI is beginning to catalog mutations, that's the US equivalent. The European equivalent is the LOVD, the Leiden Online Database of Variants (www.lovd.nl/3.0/home). Another type of database that has all different diseases but might have the CF mutation that you're looking for.

A good clue, if you can't find anything, is to look at the genetic testing lab report. Many of the commercial labs and many of the academic labs will put what's known about a mutation on the report, including links to papers or links to CFTR2. And if you looked in CFTR2, you might see that E56K is a CF-causing mutation, but it's associated with some milder phenotypes when it's been reported in patients.

MR. BUSKER: I want to let our listeners know that links to all these websites can be found in the transcript version of this podcast. This patient's other mutation, R117H, is pretty well-known. But tell us about the significance of R117H.

DR. SOSNAY: The R117H mutations gives patients and clinicians a lot of headaches because it's difficult to understand. Science worked out some of how this mutation works but it's very hard to predict. R117H is an example of a missense mutation. Sometimes it can cause CF, other times it causes no problems at all and the patient has no symptoms whatsoever and can live a totally normal life. What seems to predict whether or not R117H will cause cystic fibrosis is a genetic change that's close in the gene called the poly-T tract. This is within the intron of the gene or part of the gene that doesn't code for the protein but can tell the machinery of the cell how much protein to make.

When genetic testing labs see R117H they do a test of that poly-T tract, it's called a reflex testing. You shouldn't have to order it separately, automatically when they see R117H they should do this. And on that chromosome, on that CFTR gene where the R117H is, you're looking for the 5-T, a string of 5- thymidine residues. The 5-thymidine residues are the flavor of R117H that's most likely to be associated with CF. If they see R117H and 7-T, sometimes it causes CF, but more often than not it is asymptomatic, but if they see R117H with 9-T it's always asymptomatic. It is difficult to tell whether you're 5-T or 7-T or 9-T with R117H. In some cases, the parents have to be tested to see which poly-T tract is passed along with the R117H mutation.

MR. BUSKER: Thank you for that explanation. Let's go back to the six week old baby you described. What's the expected prognosis? And what would that prediction be based on?

DR. SOSNAY: Even with a genetic disease that has a clear Mendelian cause, there is a wide range of possibilities. This is talked about in the introduction to the eNewsletter where we pointed out that even with patients with delta-F508, there's a wide range of lung function.

So when I'm talking to patients, I'll say we don't know what to expect; some people have very, very severe disease and others have mild disease, so as much as we can do to try to encourage good follow-up, good adherence to medication, good communication with the CF team to try to maximize our chance of those good outcomes.

Let's take this patient, in particular. She has R117H and let's assume she also has 5T. That's a mutation that causes cystic fibrosis, but typically it's a milder mutation that is associated with pancreatic-sufficient

cystic fibrosis. This is the type of patient who wouldn't have to take pancreatic replacement enzymes, at least during childhood.

Lung function is very very difficult to predict, so it's very hard to say whether this patient will have mild or severe lung disease. I'd use this as a teaching point to try to encourage doing the best we can with following through with therapies and treating infection, maintaining good nutrition — all the things we know are associated with good lung function.

This patient with E56K probably has a milder mutation and R117H-5T, which is also a milder mutation. She may have cystic fibrosis — she has two mutations that can cause cystic fibrosis — but this patient has two mild mutations together, so she might not develop the symptoms of cystic fibrosis until later in life and might develop just a single organ that's a problem. She could have lung problems like bronchiectasis, or pancreas problems like pancreatitis. If this patient were male, the only way you might know that this person isn't healthy is if they have infertility due to obstructive azoospermia or sometimes called CBAVD, congenital bilateral absence of the vas deferens.

MR. BUSKER: What about testing? What tests would be useful in this situation?

DR. SOSNAY: In this case, I think the clinical tests have to take priority, and using your clinical intuition is the most important factor in deciding how to treat this baby. Some of the diagnostic tests that might be useful would be a sweat chloride test that can be done in the CF center. In general, just a good history and physical. I think in particular, attention to how the patient's doing on the growth curve. A lot of times if that patient's having problems some of the first things you'll notice will be that they're not growing, they're not gaining weight, they're not growing as much in inches as normal infants.

PFTs are tough to interpret in infants. They can be done, but it's hard to know whether problems are related to the test or to the lung. I think the most important thing is to establish a good line of communication and make sure the family knows that these are issues that you want to hear about, particularly lung problems or problems with growth, and ensure the baby has good follow-up.

We sometimes do some research tests. I mentioned the rectal biopsy before or the nasal potential difference, but it's less likely that these will be done and I think time is a more important teacher of what this patient will do than any particular diagnostic test.

MR. BUSKER: Thank you, doctor. We'll return with Dr. Patrick Sosnay from the Johns Hopkins Cystic Fibrosis Center in just a moment.

MS. MEGAN RAMSEY: Hello, my name is Meghan Ramsay, nurse practioner and Adult Clinical Coordinator for the Johns Hopkins Cystic Fibrosis Program at the Johns Hopkins University School of Medicine.

I am one of the Program Directors of eCysticFibrosis Review. These podcast programs will be provided on a regular basis to enable you to receive additional current, concise, peer-reviewed information through podcasting, a medium that is gaining wide acceptance throughout the medical community. In fact, today there are over 5,000 medical podcasts.

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Continuing education credit for each newsletter and each podcast is provided by The Johns Hopkins University School of Medicine for physicians and by The Institute for Johns Hopkins Nursing for nurses. Subscription to eCysticFibrosis Review is provided without charge, and nearly a thousand of our colleagues have already become subscribers. The topic-focused literature reviews help keep them up to date on issues critical to maintaining the quality of care for their patients.

For more information to register to receive eCysticFibrosis Review without charge and to access back issues please go to www.ecysticfibrosisreview.org.

MR. BUSKER: Welcome back to this eCysticFibrosis Review podcast. I'm Bob Busker, managing editor of the program. Our guest is Dr. Patrick Sosnay from the McKusick-Nathans Institute for Genetic Medicine and the Johns Hopkins Cystic Fibrosis Center. And our

topic is: What Does CFTR Tell Us About Lung Disease?

We've been discussing how some of the new information Dr. Sosnay reviewed in his newsletter issue can be translated into clinical practice. So please present another patient.

DR. SOSNAY: For our next patient we'll leave the pediatric clinics and go to the adult clinic, which is more my area of expertise, so I'm going to be much more comfortable. We have a 57 year old gentleman who is referred for evaluation of bronchiectasis, dilation of the airways.

He describes a history of frequent bouts of bronchitis. Usually he goes on antibiotics for these and at times he's put on corticosteroids, as well. A sputum culture grows *Pseudomonas*, one of the typical organisms that we see with cystic fibrosis, but we also see it with bronchiectasis in general. He has the CFTR genotype sent and we see that he's got one copy of F508-del and another copy of a novel mutation, G178E. You look at some of those online resources we talked about and can't find anything about G178E.

MR. BUSKER: All right: 57 years old, frequent bronchitis, and you've been asked to evaluate for bronchiecstasis. So let's start there, with the diagnosis. Does this patient have cystic fibrosis?

DR. SOSNAY: Cystic fibrosis is a clinical diagnosis, but just because he has two genetic variants doesn't mean definitively that he has cystic fibrosis. G178E is an example of what I would call an uncharacterized variant. We don't know if that's just a DNA change that doesn't have an effect on the CFTR protein or if it's a DNA change that is deleterious to the protein and could lead to cystic fibrosis.

In this case, other diagnostic tests would be useful, particularly a sweat chloride.

MR. BUSKER: In what scenarios would he not have cystic fibrosis?

DR. SOSNAY: The first situation, which is a tricky one, is we don't know if these two mutations are on the same chromosome or on different chromosomes. The term geneticists will use is when two mutations are on the same chromosome, or in the same gene, they're referred to as being in cis. If the two mutations are on opposite chromo in trans. For this patient to have cystic fibrosis, the G178 mutation would have to be on a different chromosome than his F508-del, or delta-F508.

The G178 mutation is a mutation that we haven't studied so we don't know if it's neutral and doesn't harm the protein, or if it's deleterious and interrupts protein function so that it doesn't work well. If it's the case that G178E is a neutral variant, sometimes these are referred to as polymorphisms, although that term isn't correct, he could be an example of a carrier.

Now for the most part, we think of CF carriers as being asymptomatic, but in very rare cases sometimes a carrier develops some of the symptoms of cystic fibrosis. The big question about whether we call him CF or not, because he's got at least some symptoms of bronchiectasis and the *Pseudomonas* that would go with cystic fibrosis, we would want to look at the other organs that would be affected in cystic fibrosis. We'd want to do a detailed history and maybe even some diagnostic tests to look at his pancreas, we'd want to make sure to ask him whether he's had any history of pancreatitis, we'd want to do a sweat test to see if there is evidence of CFTR dysfunction in the sweat gland, we'd want to look to see if he's had any infertility problems in his life. Sinus symptoms might be another thing that might suggest that he's got CFTR dysfunction in more than one organ system.

MR. BUSKER: Let me ask you to approach the diagnosis from the opposite perspective. What would make you clearly diagnose cystic fibrosis in this patient?

DR. SOSNAY: Bob, I would say that this person has a clear diagnosis of cystic fibrosis if he's got an abnormal sweat test or an abnormal nasal potential difference. Those are tests that directly measure CFTR function that would tell us that CFTR is not working and definitively that his bronchitis, his bronchiectasis, his *Pseudomonas* infection in his lung is due to CFTR dysfunction.

If these tests aren't necessarily diagnostic, we also might suggest that he has cystic fibrosis if he has other organ system manifestations. For example, if you can elicit a history of infertility because of obstructive azoospermia or CBAVD, or he has a history of pancreatitis, or perhaps a history of nasal polyps or extensive sinus disease.

Either of those two things, an abnormal sweat test or an abnormal nasal potential difference, are direct evidence of CFTR dysfunction; or another organ system is disrupted in the typical pattern we'd see in cystic fibrosis.

MR. BUSKER: Let's assume that this patient shows either direct evidence, or as you just said, involvement of another organ, and so you diagnose cystic fibrosis. From the clinician's perspective, in the clinic: how does that diagnosis affect his management?

DR. SOSNAY: This is a pretty challenging question, and you could argue it either as yes, it makes a difference, or no, it doesn't make a difference. Now, it's a little easier in older adults where we have this uncertain diagnostic situation. For this patient, we're not going to do too much different, whether or not we diagnose cystic fibrosis. We would treat him with antibiotics, we would use airway clearance measurements like, perhaps, Acapella valve, or at least meeting with a physical therapist or a respiratory therapist to talk about good airway hygiene and good airway clearance maneuvers.

In general, especially in the United States, making a diagnosis of cystic fibrosis is beneficial because it gets you into the multidisciplinary CF care teams. I've always said we take better care of our patients with CF than a lot of other clinics do, and I think one of the reasons is we have committed doctors, nurses, but also committed dietitians, committed physical therapists, and committed social workers, and they all know cystic fibrosis well and are all used to working with patients with problems like this.

Where it's particularly important to know is whether he has a diagnosis of cystic fibrosis is to his family, who might also carry some of the mutations. This is a situation where I would encourage his family members to be offered genetic counseling. For example, if he has children or even nieces or nephews who are thinking about having their own kids, they may carry the same *CFTR* mutation we found in our patient.

The important consideration here, and the elephant in the room with all this, is what is it going to do with regard to health insurance. In the United States we're undergoing a lot of changes in health insurance with the Affordable Care Act coming online, but a CF diagnosis would make it much more difficult for either him or his employer to purchase health insurance. So that's certainly something that has to be considered before you label him with a cystic fibrosis diagnosis.

But in general, he would probably get better care in a CF center, regardless of whether he has the diagnosis, and the treatment you'd use wouldn't necessarily be that much different whether we say he has CF or has a CF-like disease, bronchiectasis and Pseudomonas.

MR. BUSKER: A brief summation: your thoughts on diagnosing CF in this patient.

DR. SOSNAY: This patient is challenging either way. I think the diagnosis of cystic fibrosis is clear if you have an abnormal sweat test or an abnormal nasal potential difference. If you don't have those tests or if those tests don't show a clear CF diagnosis, it becomes much tougher. This is an example of patient you might consider having a CFTR-related disorder. An example of a disease that's described by the cystic fibrosis foundation and another large group of doctors who care for CF patients as being the gray area between full blown CF and healthy adults.

MR. BUSKER: Thank you for today's cases and today's discussions, Dr. Sosnay. Let me ask you to make some predictions about the future of cystic fibrosis genetics and mutation-specific therapies.

DR. SOSNAY: We're in a really exciting time in cystic fibrosis, and ivacaftor we hope is the tip of the iceberg for mutation-specific therapies. This is an example of a patient whose particular mutations allow him to get drugs specifically targeted to his type of mutation or group of mutations, or in some cases maybe even that single mutation, that will be effective and repair the defect of that mutated CFTR protein.

This gives us a way of thinking about personalized medicine in a very, very discrete example. This is, I think, the best example of personalized or individual medicine. One of the things we're learning is the correlation between the genotype — the mutation someone has — and their phenotype. It's challenging to correlate their genes and their phenotype to know how they'll do clinically. The McKone article in the newsletter discusses some of the challenges with that.

Several new therapies are under investigation, specifically therapies for mutations that cause premature termination, class I mutations and other

therapies that are specifically for the F508-del mutation. All of those therapies are under experimental trials, I'd encourage you to contact your CF center about potentially enrolling in those trials if you're interested, but the hope is that those trials will be available for patients in the near future.

Finally, I want to reinforce the point I made earlier: CF will remain a clinical diagnosis, even in the future, even as we have databases and even as we have this sort of enhanced understanding of genotype and phenotype relationships. The clinician is still very important, because looking at a patient and seeing how they're doing will tell you a lot more than the genetic testing report.

MR. BUSKER: Thank for sharing those thoughts. To wrap things up, let's review the key points of today's podcast in light of our learning objectives. So to begin: recognizing that ivacaftor is a new therapy for CF patients who specifically have the G551D mutation.

DR. SOSNAY: Remember, as we talked about in case one, ivacaftor is a therapy specifically for patients with cystic fibrosis who have at least one copy of the G551D mutation.

As the Ramsey article pointed out, discussed in the newsletter, it's been associated with improvement in pulmonary function, fewer CF exacerbations, improvement in weight, improvement in sweat chloride, and improvement in the respiratory questionnaire score that tracks how patients are doing from day to day.

Encouragingly, the side effects of this medication seem to be similar to those of placebo, but it's a new drug, so of course we'll need to watch it as patients are on it for longer periods of time.

MR. BUSKER: And our second objective: how CFTR genotype influences lung function.

DR. SOSNAY: We didn't specifically talk about this in the cases, but one of the reasons we didn't is, it's very difficult to predict. For example, the infant in case two who had a positive newborn screen, it's very difficult to predict what the lung function will be. There's a wide range of possibilities, and the CFTR genotype doesn't necessarily tell us exactly what the lung function will be in five years, 10 years, 50 years.

The other side of that is the patient we described in case three. He had evidence of lung disease but we didn't know whether his lung disease was due to CFTR dysfunction or just bad luck and chance and maybe something in the environment that caused bronchiectasis and exposed him to *Pseudomonas*.

So CFTR genotype is tremendously important, but it can't predict lung function.

MR. BUSKER: And finally: using CFTR genotype to help diagnose cystic fibrosis, predict prognosis, and select therapies.

DR. SOSNAY: As I said, CFTR genotype is not useful to predict lung function, it is still useful and will become more useful the more we know about this disease.

Specifically, we can use *CFTR* genotype to help us make a diagnosis of CF. If someone has two known, bona fide CF-causing mutations, that should instruct the clinician to look hard, that that patient likely has the other clinical symptoms that would go along with cystic fibrosis.

The other way that genotype is useful is, it allows us to make some general predictions about the prognosis of a patient. We won't be able to say exactly what the lung function will be, but we have a good idea whether the patient will be pancreatic insufficient and what to expect over the course of the lifetime in someone who has severe mutations versus milder mutations that are often associated with pancreatic- sufficient disease.

And our hopeful future is that CFTR genotype will allow us to choose therapy. The future is here now for ivacaftor and hopefully the future is coming soon for patients with F508-del and other mutations.
This also teaches them what foods are high in calories and which ones would be good and get the most calories per bite.

MR. BUSKER: Dr. Patrick Sosnay from the Johns Hopkins Cystic Fibrosis Center, thank you for participating in this eCystic Fibrosis Review Podcast.

DR. SOSNAY: Bob, thank you very much for giving me this opportunity. I know this genetic stuff is tough and I do it every day, so I can certainly relate with the average CF clinician who doesn't have much exposure to this, but hopefully this podcast and the newsletter

have been helpful to the clinician on how genetics will be used in the future of cystic fibrosis.

MR. BUSKER: This podcast is presented in conjunction with eCysticFibrosis Review, a peer-reviewed CME and CNE-accredited literature review emailed monthly to clinicians treating patients with cystic fibrosis. This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing.

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