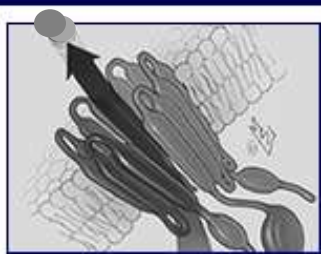
AHEAD OF THE CURVE
EMERGING CF THERAPIES 2009



**Transcript: Managing Patient Expectation: Christopher H. Goss, MD, MS**

DR. CHRISTOPHER GOSS: Thank you very much for having me. And so I am going to talk a little bit, a sort of divergent topic, it really is, the challenge is managing expectations and then we'll present some case scenarios, which I think good case scenarios have no clear answers, so hopefully it will have no clear answers.

So this is my disclosures, but I wanted to show the pipeline because this is our new problem. I think when I started as a fellow there weren't many of these lines or bars in this chart, and this is the number of new therapeutics coming into phase II/phase III trials, and our ability to sort of, the challenges of meeting the needs of these trials but also interpreting the results and integrating the care is not trivial for CF, it's a great problem to have, but it can be challenging.

I think there have been a lot of exciting developments in CF. This is just from the *New York Times,* Rick Boucher (UNC-Chapel Hill) said in relationship to the VX story, "I do think we will see a cure, these therapies that hydrate the CF airway surface," this is, I'm sorry, inspire, "be able to stop the progression of disease in adults and I am very excited in babies that you may be able to help prevent the disease." This is both for all these new therapies.

*The New Yorker*, this is a CF patient, Chrissy Falletti, who is in the Vertex trial, who after 28 days of drug, on the medication, her lung function had increased 18 percent. Her lung function began to climb within a week of the trial's end. So this is patients' perceptions of these trials and this is widely distributed in the common press.

So patient expectations, we really don't have any empirical evidence of what patients' expectations are, however, I would argue that they are very high right now. Enrollment in the VX770 was extremely rampant. Many sites actually, we were one site, we had a hard time even getting a single patient in because it almost closed before our patients could be enrolled.

VX809 is already closed. So when trials open and close quickly, it tells you there is a lot of excitement in the CF community. I do worry that this may be analogous to expectations in the early '90s with the discovery of the gene. If you remember liposomal delivery of CFTR corrected conductance defect in CFTR null-null mice, and this is a statement that came from nature. So there seems to be no reason why this approach should not be transferable to humans. And actually later in the article they intimated in short-term. So we should have gene therapy to cure this disease in short-term. And we are now, this is obviously years, a decade later and we don't have gene therapy. So I think we all have to be somewhat cautious in our interpretation of clinical trial results and new scientific advances.

Now there are a lot of challenges to clinical research in CF. The population is limited. You cannot address more than a handful of important questions. And as you see by that pipeline, there is a lot of research ongoing. It requires many studies, to do any single study you need many centers. So this really increases the cost of doing clinical research.

Important outcomes like lung function decline and exacerbation rate lead to large sample size. As you saw, the Denufasol study is 450 patients, much akin to the DNA studies. Therapies that correct the basic defect will require long-term follow-up to really assess their impact, and this may, if you want to look at any drug that affects survival, it really can't be studied in CF. Survival rates are very good, fortunately in CF.

So just to give you a little historical perspective on the clinical trials network, this is the US Therapeutics Development Network started in 1998 with 8 centers, and they have done more than 50 therapeutic clinical trials and enrolled more than 3,150 and patients in CF pediatric and adult trials during the last 5 years, and that's a lot of patients for a rare disease. If you go talk to your colleagues who study other rare diseases, this is overwhelming in the sample size that we've been able to generate from a very supportive community.

The network expanded in 2009 to 77 centers, and now, you know, there are 30,000 patients with CF in the United States and approximately 19,000 of them are cared for in these 77 therapeutic centers. So a huge proportion of CF patients are actually in these centers doing clinical research in CF.

But we do have some serious challenges. So for the 77 sites, which have about 19,000 patients, the educated estimate for the 2008 enrollment was 1,160. So

the percent of enrollment was about 6 percent of the total patients. And when we look back in 2008, some sites enrolled as many as 16 percent of their patient population, others only 1 percent. So there's a lot of variability of which centers participate aggressively in clinical research, which patient populations are willing to participate in clinical research.

The TDN, we do estimates of sample sizes that we're going to need for the following years, and in 2009/2010 we approximate, 2,300 patients, about 12 percent of all the patients seen at these TDCs. So that's almost twice the enrollment rate seen in the last year so that's a big change to meet the needs to bring these new therapies to CF patients.

And I think they are important challenges for investigators. The enrollment needs are high, given the numbers of studies. There's a lot of study metrics now, the coordinating center follows, I'm at the University of Washington, we get our metrics, we update our metrics every month. So we're following are we enrolling enough, are we participating enough, so there's a lot of close study of how quickly we get studies going, how quickly we get patients into studies.

Investigators overseeing studies are competing for the same patients, so that in one site you might have multiple studies competing for the same patients. And this is a challenge that sites have to deal with. And the other I think real challenge is the increased expectations of patients and new compounds. That new compounds will represent a cure. So what do you do when these exciting results come forward and how do you manage those expectations of patients. I don't have any concrete answers for you, but I think the discussion of some of these cases will help lead to how some people may address this problem.

Well how do we usually weigh results or evidence in clinical medicine? In the ideal world we weigh evidence using multiple sources, systematic reviews, a Cochrane collaboration. More recently, the Cystic Fibrosis Systematic Reviews, which have been ongoing in the last two years, two to three years actually. And this is just an example of the great recommendations that came out of Patrick Flume's (Medical University of South Carolina) paper published in the Blue Journal in 2007. And this was looking at the summary of recommendations for chronic therapy. And what they tried to do is a balanced recommendation based on the quality of the evidence and the benefit. And between the quality of the evidence and the benefit you get an overall grade that goes from A to D. And this is using standardized recommendations

for systematic reviews.

But what you can see is inhaled TOBI had good evidence with substantial benefit, graded A, for severe disease, mild disease it was fair with moderate, that got a B, a recombinant DNAse, A and B, inhaled corticosteroids in patients 6 to 18 years old, the evidence was felt to be fair with zero benefit with a grade of D. So again, this is actually, if you think of cardiology, they will have thousands of patients to weigh these recommendations.

I'll just give you an example of more recent work that has come out to say how we, you know, what do we do when we practice. Strong evidence is often really challenging to obtain in CF. So a recent systematic review for the treatment of acute pulmonary exacerbation, which is in press, and Patrick Flume, again is the senior author and this is in press in the Blue Journal, no therapy received a grade of A. So the thing that I spend every week year round doing, there is no grade A evidence for me to sort of guide my therapy.

Only two questions received a grade of B, which is continued chronic use of therapy. You know chronic therapies during exacerbation and use of airway clearance, and those came from the prior recommendations. The remainders of the evidence received a C, D or I gradation.

So what do physicians do in the setting of no evidence, how do we practice? Well I think this is particularly problematic in pediatrics, because there has been a dearth of studies in children. There is a lack of pediatric studies, may increase off label use. It certainly does in adult medicine.

It's an interesting study that was, there's a survey of inpatient pediatric wards in the United Kingdom, Sweden, Germany, Italy and the Netherlands, and they found that greater than 50 percent of the children, so 67 percent received an unlicensed or off label medication during their hospital stay. And this is just all hospital stays. I actually would argue that it is probably more common in the United States. And there is absolutely no date to suggest how often we're doing off label use in CF.

But how much evidence is necessary to apply new therapies in CF? In this I go to a paper written by Dr. Mark R. Tonelli (University of Washington Medical Center), who is in our division in respiratory care, spent his academic career focusing on ethics and also on weighing evidence based medicine. And there is always a gap, a gap always exists between the empiric evidence and patient care. And that should be understood.

Patients' expectations have to be integrated into decision making when you are going to use off label therapy. They have to understand the risks and benefits of an off label agent where risks and benefits may only be poorly understood.

Study results also importantly almost, you know, ideally, study clinical trial patients are selected for clear reasons; they have clear inclusion/exclusion criteria. We often don't use those inclusion/exclusion criteria when we apply the agent in the study population. So often we're trying to decide how to apply these drugs to our patients and we have to think what is the best for the patient at hand.

In general it goes back to the clinician to try to make a balance, but most importantly to do no harm. And this is the mantra I use in my clinical practice, whatever I do, I don't do harm.

So I think there are some important challenges that we have to face in CF and I think they are coming real soon. And these are some of the questions that I don't have any answers to. Can one extend use down to infants, so an agent that is studied in small children but not infants? This is a population not studied in many studies. Could it be used, so let's say you have a genotype specific agent, could it be used in a patient with a different genotype? We have already had a question just based on that same identical issue. Can the agent be used beyond a study window; we do that all the time for azithromycin right now. It's a six month study window, I have patients on it who have been on it since 2003, since the paper was published.

If it is employed in a non-labeled population how do you monitor its use? Can one apply study drugs to different severities of illness. So can we use a drug in a patient with severe disease in which the study population never had severe disease? I think these are really challenging questions that we don't have good answers to but we tend to leave to the clinician to figure out.

I'm going to sort of conclude and then we'll present some, I think some clinical scenarios and try to get some discussion on these points. My conclusions are I think there are some dramatic advances in CF and I think the enthusiasm is terrific. I think we do have to manage expectation. I think we have to remember the time to gene therapy and realize that the cure may not be right around the corner. I think clinical trials remain the key to advancing our knowledge, and without clinical trials in CF we will have absent knowledge.

I think our enrollments are going to be very high over the next, you know, one to five years, and we are going to have to manage those expectations of those

patients so they can actually be integrated in clinical trials. And then integrating the results of clinical trials into clinical care will be really challenging, and I think a challenge that we are actually fortunate to have.

I remember I actually gave the plenary session at the CF meetings and I think Bob came up to me after and said, boy, it's so easy now because we actually have some therapies that work. I think for years they gave up and had plenary sessions where they had no trials to present. And now you look at today's plenary session and yesterday's plenary session where we talk about these endless numbers of molecules and approaches, but it's a challenge, a great challenge, but I think it is going to be hard for all of you in the field to figure out to deal with that challenge.