Pulmonary Hypertension Roundtable

Importance of Early Diagnosis

During the American Thoracic Society’s International Conference 2012 in San Francisco in May, Dr Greg Elliott, guest editor of this issue of *Advances in Pulmonary Hypertension* on early diagnosis of pulmonary hypertension, invited Drs Marc Humbert, John Newman, and Julio Sandoval to convene one morning for an invigorating discussion relating their experiences, concerns, and suggestions for strategies to improve time to accurate diagnosis of pulmonary hypertension.

**Dr Elliott:** I’m Greg Elliott. I’m Chairman of the Department of Medicine at Intermountain Medical Center and a Professor of Medicine at the University of Utah. And today, we’re going to talk about delays in the diagnosis of pulmonary arterial hypertension and the possibility of making the diagnosis earlier. I’d like the panelists to introduce themselves, if you would, please. And I’ll try to do this in alphabetical order, which I think puts Dr Humbert first.

**Dr Humbert:** Good morning. My name is Marc Humbert. I’m a respiratory doctor at the South Paris University. I am the Chair of the Research Institute on Pulmonary Hypertension from the South Paris University and I’m also a clinician and consultant at the French Reference Center of Pulmonary Hypertension.

**Dr Newman:** Hi, I’m John Newman. I’m at Vanderbilt University in Nashville. I’m a pulmonary and critical care doctor, Professor of Medicine, and Vice Chairman for Faculty Development.

**Dr Sandoval:** I’m Julio Sandoval, from Mexico City. I’m working at the National Heart Institute; I am at present the Deputy Director of Clinical Research at this institute, and I have been working with pulmonary hypertension for many years.

**Dr Elliott:** I think it’s nice to say that collectively in this room, there’s a lot of experience with this disease. And we’re going to tap that experience in this roundtable discussion. I’m going to give some background and start by saying that the issue of delays in diagnosis, I’ve always thought of as an elephant in the room. We just haven’t talked about it much before. And yet, it’s a really important subject for us to pay attention to. In many ways, it has been the patient’s story, because our patients tell us about seeing one or another physician or telling someone about their condition, and no one can quite diagnose it or they’re given some other diagnosis. And yet, it’s our responsibility, I think, to get the word out and help our colleagues to make the diagnosis earlier. The truth is that delays in diagnosis of Group 1 pulmonary arterial hypertension are very common and they’re often prolonged. In the original National Institutes of Health Registry, conducted from 1981 through 1985, the median time from symptom onset to diagnosis was 15 months. And by the time these patients were diagnosed, three-fourths of the patients were functional class III, meaning they had very advanced disease. Investigators in the REVEAL Pulmonary Arterial Hypertension Registry, conducted in 2006 and 2007, found a median time to diagnosis of 14 months. So over that period of time, in spite of advances in treatment and a lot of publicity about effective therapies in professional journals and elsewhere, the time to diagnosis didn’t really change very much. Perhaps of even more concern, 1 of 5 patients had symptoms for 2 years or more before they were ever diagnosed. And I think we’ll come to the point of understanding that sometimes patients come to us so very late in the disease that we cannot intervene effectively. And their disease hasn’t been recognized, which is always a concern.

Recently, there’s a publication from the REVEAL Registry by my colleague Lynn Brown, where she tried to look at what some of the factors were that were associated with delays in diagnosis. And Lynn reported that age under 36 years was actually the factor that most commonly identified an increased risk for delay in diagnosis; and that odds ratio was a little over 3. A history of obstructive lung disease was also associated in the REVEAL Registry with a delay in diagnosis. And I know many of you have seen or heard the story of a patient with severe pulmonary arterial hypertension coming to you, having been diagnosed and treated for asthma for some time. Sleep apnea also was a common masking diagnosis or misdiagnosis of pulmonary arterial hypertension, perhaps reflecting our obesity epidemic in the United States. It would be interesting to hear what the experience is in Europe and France and Mexico. There were also some factors that weren’t associated with delays in diagnoses. Interestingly, neither women, nor racial, nor ethnic groups were at increased risk for diagnostic delays. Four broad geographic regions of the United States were studied. Whether it was West, Midwest, Northeast, or Southeast, the delays were pretty much the same in each region. And the initial physician who saw the patient didn’t seem to matter very much either, whether it was an internist or a pulmonologist. Delays didn’t seem to be particularly common with any specialty. So I think the theme is that delays in diagnosis and treatment of
Group 1 pulmonary arterial hypertension are just not acceptable in an era of effective therapy. And we really have to do something to make the diagnosis more promptly.

Dr. Humbert: I’d like to start with you, because you and your colleagues also describe delays in diagnosis of pulmonary arterial hypertension in France in the French Registry. And what I found in your report was that there was a delay from symptom onset to diagnosis of 27 months. Maybe that was the mean delay, not the median. And a majority of patients had severe symptoms at presentation, so it sounds very much like the United States experience. But what have you learned about this subject in France?

Dr Humbert: Thank you. It’s indeed the same problem as in the current US registries. We have most of our patients presenting with advanced disease. Three-quarters at first diagnosis are in functional class III or IV. And most of them have been symptomatic for more than one year. If you analyze the 2002/2003 period of the French Registry, the mean delay was 27 months, with quite large scatter, of course. But still now in the very modern management era, we have a majority of patients diagnosed more than one year after first symptomatic evidence of the problem. Thus, there is a delay in management of the disease which could be avoided if early diagnosis was established, because all the drugs we have for pulmonary hypertension are approved for symptomatic pulmonary arterial hypertension. So by definition, if they had symptoms, they should be considered for therapies. In addition, we know better and better that early intervention translates into better outcomes, at least from randomized controlled studies and registries. So the situation in France is pretty similar to the situation you just summarized: a long delay before confirmation of the diagnosis and a very long period of symptoms that are often overlooked because the patients either look fine or because they have a so-called co-morbidity, which is often not the case. As you emphasized, asthma is often considered as a cause of shortness of breath, although there is often no robust evidence of asthma in these patients. And the patients are treated with inhalers, without any clear symptom of asthma. Because they are refractory to this treatment and because they express more and more difficult symptoms, they are then redirected to specialists. So I think the major take-home message from the French Registry is that robust diagnosis of any cause of dyspnea is mandatory: asthma, COPD, left heart failure, anemia. So it’s too easy to say, well, you’re young, you don’t wheeze, but you have asthma, because asthma is common in young people. Moreover, when you measure the pulmonary function of these patients, sometimes in PH they have a small distal pulmonary airway obstruction; but this is not asthma, it is just a possible finding in pulmonary hypertension.

Dr Elliott: I wanted to just follow up on one of your points and say one of the things I’ve always said is that, often, the patients do look well. And I think that fools doctors quite often. I wanted to follow up, too, on your description, Marc, because the parallels are striking. In the United States, many young adults do not have health insurance. You know, once they leave the umbrella of their parents’ health insurance, they may go for a period without good health insurance, which might delay their seeking care. And that might be part of why the younger ones were more prone to these delays. Do you have any sense about whether young patients in France are also more susceptible to these delays? The insurance system wouldn’t be the same in France, if I understand it correctly.

Dr Humbert: In France, everybody is covered by insurance, even the homeless. I mean, there is a global organization that supports everyone. Thus, any young adult can go and see a GP, a cardiologist, a pulmonologist, etc. But sometimes when they have a diagnosis established by a doctor—which might be wrong sometimes—they often do not go and seek other advice, because they think that the diagnosis is done. So I think in France at least, the problem is not health insurance, it’s more awareness of the community and awareness of the front liners, the GPs and the specialists in the community. And, of course, we’ll touch that later but I think our task with GPs is to emphasize that the cause of any shortness of breath should be robustly diagnosed and identified.

Dr Elliott: I think you make a good point. The young people often are the ones that can look quite healthy, as well. So they do look well and it’s easy for a GP to say many if not most of the patients who come and they’re young and breathless, they’re going to have asthma. So, as you said, a robust diagnosis is critical. Is there any hint in your data or do you have any hint that gender, race, or geographic regions are particularly problematic in your country?

Dr Humbert: Well, we don’t have direct evidence of that and we have the same feeling as the REVEAL colleagues. However, if you analyze the prevalence of pulmonary arterial hypertension in rural regions and small cities in France, you realize that there are marked differences with larger cities. For example, in Paris, in Strasbourg, where you have very strong university pulmonary vascular centers, the prevalence of PAH is 25 per million. If you go to more rural areas
of the country, the prevalence ranges between 5 and 12. There is no good reason to explain such a marked difference between rural areas and cities. I really think that there is a missed population of patients we cannot analyze in our registry. There is thus a clear difference in terms of prevalence, which may reflect the lack of awareness in some places. However, I have no direct evidence from our registry that there is any kind of problem with gender, age, or race.

**Dr Elliott:** Julio, you and your colleagues in Mexico City see many patients with pulmonary arterial hypertension. Are there similar delays from symptom onset to the diagnosis in Mexico?

**Dr Sandoval:** Yes, Greg. The situation in Mexico is similar. Just to give you an idea, in the ‘90s when we didn’t have specific therapy for treatment, the time between symptoms to diagnosis was about 4 years. We published that in a paper in *Circulation* in 1994. Now in the last decade, that we have been participating in clinical trials and we have at least some form of treatment, the time from symptom to diagnosis is still about 2 years. And again, a significant proportion, probably 50 to 60% of our patients, comes to us in functional classes III and IV, which is disappointing. Regarding misdiagnosis, we also have the same experience. Of course, asthma in the respiratory community is a frequent misdiagnosis and actually many of our patients are also treated with bronchodilators, without success, before the diagnosis of PH is established. Other common misdiagnoses are obesity, which is becoming a problem in our country, deconditioning, anxiety, dysautonomic disorders, and panic attacks. I mean, they are diagnosed as many other things and they go through a series of studies and many consultants before diagnosis. So, part of the delay in diagnosis in Mexico is lack of awareness not only in the public, but also in the medical community. Lack of economic resources to look for medical attention as well as late referral to specialized centers is also another reason for delay in diagnosis.

**Dr Elliott:** So we’ll come to this, I think, but one of the issues for all of us is how do we build awareness in the medical community and in the public at large. One area that I have always found particularly disturbing is when we learn of pulmonary arterial hypertension patients or Group 1 patients who come to medical attention very, very late in the disease. So late, in fact, that it’s too late. And I wondered if each of you have had this experience or seen such cases and what your observations were and what you think might have been done to catch the disease earlier in those cases. Is there something that characterizes those cases, a common denominator? Julio, why don’t I stay with you for a second. Have you seen people who came to your attention just too late in the disease?

**Dr Sandoval:** Yes, Greg. As I said, almost 60% of our patients come to us in a late stage of disease, and not enough awareness in the medical community is one of the main problems. So, the best thing we can do in order to improve this situation is to increase awareness. Every doctor, no matter what specialty, should take into account the diagnosis of pulmonary hypertension in every patient that, as Marc said, is complaining of exertional dyspnea or fatigue. We should also think about the possibility of building some kind of guidelines for the assessment of shortness of breath in patients with exertional dyspnea as one of the ways to go. Another problem in my country is that we don’t have enough referral centers. For the whole country, there are about 6 centers only and most of them are in Mexico City. There is one in Monterrey, which is located in the north part of Mexico, and another is the center of the country. So, patients have to travel long distances to look for medical attention once someone has the suspicion of pulmonary hypertension. Increasing the number of referral centers is something that we can do in the near future in order to catch the disease earlier.

**Dr Elliott:** Marc, do you see these patients with extreme delays in the diagnosis, and is it too late?

**Dr Humbert:** Yes, indeed. There are 2 major presentations. One is longstanding ignored symptoms, coming too late to the ICU in our institute, in late class III, or class IV. The other situation is a kind of malignant form of very rapidly progressive pulmonary arterial hypertension, certainly because of failing right heart. We are quite fortunate in my country because France is very organized in terms of rare diseases, with a network of centers throughout the country. And we receive in Paris the most severe cases, which should be considered for very active management. Still now, we have 15% of patients diagnosed in class IV, which is very, very late. For these patients, we consider very expensive management such as upfront combination therapies and lung transplantation. When we analyze the history of these patients, there is always a missed opportunity, and that’s what I want to emphasize. Often, these people have been, for example, short of breath after a pregnancy, or after gaining some weight and their doctor and family may say, “Well, you’re not fit enough, you have to exercise.” We have quite a lot of patients who could have been diagnosed in class II, which is our goal, or early class III, who are indeed seen for the first time in late III or
IV. More and more, we try to identify these patients to see where and when was the missed opportunity. Usually the missed opportunity is either, as you said, misdiagnosis at baseline, or lack of awareness of pulmonary vascular diseases. We see too many patients late in the course of the disease. It is still, I think, dramatic. And we have to do what you are doing right now, increase awareness of the community on early disease.

**Dr Elliott:** Given your referral center and expertise, I wonder, although this isn't exactly the delay in initial diagnosis, do you see patients who now are placed on oral therapies and then there's perhaps too much time delayed before they're referred on to your center for advanced therapies, like the parenteral prostanoids? And I'm going to turn to my colleague, Dr. Newman, as well, and ask about whether you see that at Vanderbilt; I think that's always been a concern in the United States.

**Dr Newman:** We still see patients that come in at the end and die quickly. And we see it not only with idiopathic pulmonary hypertension, we actually had it happen in a family member about 6 months ago, which was very disturbing. The diagnosis should have been obvious to the patient and his doctors. He came into another hospital in Nashville and died before we could help him. So, I think I agree with everything you guys have said: we have to get pulmonary hypertension in the differential diagnosis of dyspnea and loss of energy, which are the 2 things that these people show up with. Just like oximetry is becoming a vital sign, we need to have some sort of sense of, okay, what do I do to be inclusive in a patient that has dyspnea and loss of energy and they're a young person, usually a woman. You've got to go farther and that's just not being done.

The interesting thing about this young man was he was in a family and we had a big discussion after his death, and we'll get to that, about whether we should have forced the family to have genetic testing, because Jim Loyd thought that this would have saved this young man's life if he'd known he had the mutation. So the answer is yes, it's very vexing. The doctors don't think of it and sometimes the patients don't pursue it. I think partly it's because they look so normal. Doctors just won't believe there's something wrong with them.

**Dr Elliott:** John, we had the exact same thing happen in Salt Lake with a young woman. And she had been told she had asthma for 3 years. Unfortunately, there was one other family member affected, so the other family member, of course all too commonly, was an idiopathic and, unknown to anyone, was the possibility that another member would have PAH. So I don't know, to be honest, if that mother who had been on Flolan had either been told or had absorbed or failed to absorb the fact that it was because she was an idiopathic; it was possible that she really was a hidden familial or heritable. But, in fact, her daughter came to us too late for effective treatment. How can we reduce these delays from symptom onset to the diagnosis? And are there similar paradigms for other rare diseases that we could learn something from? Any thoughts there, Marc?

**Dr Humbert:** You have 2 situations, of course. One is the idiopathic, sporadic case. The other one is patients with comorbidities which increase the risk of developing pulmonary vascular disease. Indeed it is easier but still quite complex to manage the people with comorbidities at increased risk of pulmonary hypertension. In those patients, I think the community and the patients themselves should know the possibility to develop a pulmonary vascular disease and the possibility to benefit from early diagnosis and screening or early detection approaches. The most characteristic situation is systemic sclerosis. We know that these patients in their lifetime may develop symptomatic pulmonary hypertension in around 10% of cases. In those patients, it is recommended to perform a clinical assessment and echocardiogram every year. Using echo-based strategy, we have been able to show that we can make early diagnoses in these populations. We have worked a lot on the patients who have been diagnosed earlier than they would have been without screening or early detection. We have analyzed long-term outcomes of these patients and compared these outcomes in people who have been diagnosed on a routine basis. Long-term outcome, 8-year survival, is markedly different between these 2 populations of patients: in case of routine diagnosis, 8-year survival was less than 25%, while in the early detection group more than 60% were alive at 8 years. This study has, of course, limitations, but it is encouraging. However, I would like to emphasize some biases. First, lead-time bias: you may identify people early, because you look for the condition, but not modify the outcome with your intervention. Another bias is length-time bias: you may identify people with a condition which is not progressive. Last, overdiagnosis is a problem. So when you do screening, it should be in the context of a very well-structured organization, with clear information.

**Dr Elliott:** Marc, those are excellent comments. And when I asked the question, I asked about parallel diseases. While it's not quite the same, your comment...
about the critical issue of over-diagnosis could be reinforced by lung cancer screening. As you know, low dose chest CT scanning is now done to find lung cancers earlier. What happens there, as you know, 1 of 4 individuals had something found on their low dose CT. Most are benign conditions. The other issue is the lead-time bias that you discussed. Sometimes those lung cancers are very slow growing and they’re relatively benign; they aren’t quite the same as aggressive forms of the disease that we’re most familiar with. So I think there are parallels whenever we get into screening of over-diagnosis, which has its own set of consequences. We have to be well informed about that issue. And then the lead-time bias is, as well, an issue.

Dr Humbert: In scleroderma, over-diagnosis is very important because you often have patients with diastolic left heart dysfunction. One should emphasize that in my screening approach, the gold standard is always right heart cath. Of course, we screen with echo, but when the patients are likely to have pulmonary hypertension, there is a need to do right heart catheterization to make a clear diagnosis. It would be dramatic to say that we screen with echo and that’s it. It is mandatory to confirm diagnosis with right heart cath.

Dr Elliott: I wanted to give Julio and John a chance to comment. And then at the same time, perhaps add something about education in addition to screening. So educational programs could be part of the way forward here, as well.

Dr Sandoval: Thanks, Greg. I support that view of doing screening. As Marc said, screening leads to early diagnosis and early diagnosis leads to good results in terms of functional capacity and hemodynamics. However, diagnosing PH in the basis of only one echocardiogram is becoming a real problem in Mexico. Many of the patients are treated with sildenafil, which is widely available in the country, based only on the results of this study. In many instances, there is no attempt for confirmation and the patient receives this single drug on a long-term basis without a formal follow-up of the result of this treatment. This is another reason to explain why many patients arrive to the referral center in a late stage of the disease. I completely agree with you, Greg, that education of the medical community has to be one of our goals to pursue. I mean we need formal programs of education not only about screening but also about the importance of diagnosis confirmation. This will be certainly one of my goals for the near future.

Dr Elliott: I think you and Marc have both empha-
penicillin for pulmonary hypertension, everybody would get the test. So it’s like the old days in HIV, when there was no cure for HIV, no one wanted to know. As soon as HIV got a treatment, everybody needed to know and wanted to know. The way people think has to do with the way medicine can help them or whether medicine is impotent to help them. So, we discovered that they didn’t want to know; a lot of them just didn’t want to know.

What we also discovered was that you must tell people that there are risks for knowing. For instance, we had this happen in one of the very first families we counseled. A young woman had it. Her mother’s sister, her aunt, died of pulmonary hypertension and one of the aunt’s children died of pulmonary hypertension. And they were very close and this was very disturbing, because she saw her loved ones die. So she knew that she had a chance of having the mutation on her side of the family. And she wanted to get married and have children. And her anxiety led her to want to get genetic testing. Well, when we talked to her about it, it became apparent to her and her father and mother and her sibs that if she were tested and found to carry the mutation, that would mean that all of her sibs had a 50% chance of having the mutation, and that her parent had it. And so her testing was not in the abstract or a vacuum; that it would impact the lives of her immediate family dramatically. And she decided not to be tested, because no one wanted to know, outside of her. The other thing we’ve had is people with the mutation decide to go ahead and have children, because they’re alive with the disease and they value their lives. Even though we know they’ve got a fatal disease based on a genetic mutation, but they’re alive, they love, and they want to have children. They have children with a 50% chance of carrying the mutation and a 20% chance from that of having disease. You can’t live other people’s lives and you can’t make assumptions based on your sense of a disease about how people are going to respond when they are confronted with it. But it is completely true that the best thing you can do is offer genetic testing and demand that they have genetic counseling prior to the testing, so that they will be fully informed about the risks and benefits about what they’re going to discover. And we’ve had some very tearful counseling sessions with families, where we’ve revealed that none of them has the mutation and a great deal of relief and also sort of guilt-related tears that they don’t have the mutation. We’ve had some very sad moments, where we’ve told people they have the mutation. The idiopathics have about a 10% risk of carrying a mutation. That’s something that we simply can’t address yet, because it’s a very expensive test. The gene is huge. It’s got 13 exons. It’s 6 million base pairs. If you don’t know that somebody has a mutation, you’ve got a huge sequencing problem. And you’ve also got to look and make sure that the other TGF-β mutations and endoglin and SMADs are not there, if you really want to be complete. And that’s a couple thousand dollars. And then the likelihood is only 10% that somebody carries a mutation. So people haven’t done it. If you have the known family mutation, you can go right to that exon and test and so it’s much cheaper. In the United States, with all of its incredible complexity of payment schedules, the test might cost the person anywhere from a couple hundred dollars to a couple thousand. It’s up to $2500 if you get the test without the known mutation. So it’s been a very interesting trip for us to figure that we had discovered something of great power with regard to peoples’ lives and then discovered that it’s not as simple as it appeared to be and continues to be complex. But the other thing is that families move away, they don’t know that they’re in a PH family. In the United States, people move. Their contact with relatives disappears very quickly. Most of the people in our families are completely unaware that they have a familial disease.

Dr Elliott: John, you know, with the complexity that you described, and people moving, I think with the cost of whole genome scanning coming down, we could see people being scanned, not for the specific gene or the 13 exons, but their whole genome, and then finding a BMPR2 mutation, and then wanting to know what we know about it. But your lead in was great. You talked about people going ahead and having children. Well, Dr Humbert’s group has now done at least some work with pre-implantation screening, so that one could go ahead and, in the right circumstance, have a child and eliminate the possibility that that child will have a BMPR2 mutation. And maybe we could close with a comment about that, Marc.

Dr Humbert: Thank you. First, I would like to say that I share every comment of John. It’s not as simple as it appears to give genetic counseling in such a complex, low penetrant, heritable condition. In France, people don’t pay for genetic screening, which facilitates, of course, the possibility to be screened and there are many PAH patients who want to know if they carry a mutated gene. But I agree with you that it is mandatory to spend time before doing any genetic testing, because they should be fully informed that we may not give them a very simple answer. Every case is a unique scenario. In a family with heritable disease, we have had several dramatic pediatric cases, and occurrences in young adults. We have fully characterized the genetic background of this condition in

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Dr Elliott
that family (BMPR2 mutation) and we have offered genetic counseling to the whole family. Among the carriers, some came and said: “Okay, I accept the risk for myself, but I cannot bear the risk for my kids. And they, of course, read the press and they realize that it is possible to do in vitro fertilization then screen the embryos to identify those carrying and not carrying the mutation. You may then re-implant in the future mother the embryos that are free of the mutated gene. This has been discussed with the ethics committees, as it is very rare to offer a pre-implantation diagnosis in a low penetrance condition. But it was considered that in this very family, the BMPR2 mutation has a high penetrance with dramatic cases. The family was well informed. They really wanted to benefit from pre-implantation genetic diagnosis. This led to the birth of a young baby boy, free of the mutation. The parents are really relieved and they consider it was good for them. But I understand there are many, many ethical issues. This case report has been published in the June 2012 issue of the European Respiratory Journal. I must say, we are happy for the families who wish to have this possibility. Of course, it’s not mandatory. You can be tested or not. You can have pre-implantation diagnosis or not. But I think it’s nice to be able to propose that to the families.

**Dr Elliott:** Marc, I want to thank you. And I’d like to bring us to a close, perhaps closing even the loop, and just say again, these delays in diagnosis are really the patients’ stories. And yet, we as health professionals who care for the pulmonary hypertension community, I think, have a responsibility to do everything that we can to advance earlier diagnosis in an era of effective therapy. And I think we’ve talked about some of the pitfalls of over-diagnosis that will undoubtedly accompany such a campaign. Awareness, I think, is important. The Pulmonary Hypertension Association is going to launch an early diagnosis campaign, which I think will be very important in getting the word out in the community. And I’m hopeful that the delays in diagnosis that have stayed with us for over 3 decades now, in spite of the development of effective therapies, will someday no longer be the case for this uncommon disorder. Rather, patients at risk will be identified, and monitored, and screened, and diagnosed if the disease begins to rear its ugly head. And our colleagues in the community will recognize this disease as a disease that can hide there alongside of the many patients they see with asthma and obesity and sleep apnea. And the colleagues will actually think of pulmonary hypertension when they see people who complain of breathlessness and fatigue that’s out of proportion, perhaps, to any asthma that they might have. Or, Marc, as you said, our colleagues will make efforts to make robust diagnoses when they diagnose asthma, to be sure about the diagnosis. So in closing, I just want to thank Drs. Humbert and Newman and Sandoval for their active participation. This has been a terrific roundtable. Thank you.