# Behind the Scenes at the World Symposium on PH 2018

This fall, Guest Editor Erika Berman Rosenzweig, MD, Professor and Director of the Pulmonary Hypertension (PH) Comprehensive Care Center at Columbia University Medical Center, gathered a group of PH specialists by telephone to discuss some key events and topics from the World Symposium on PH 2018. The participants included Vallerie McLaughlin, MD, Professor and Director of the PH Program at the University of Michigan; Greg Elliott, MD, MACP, Chairman of the Department of Medicine at Intermountain Medical Center in Murray, Utah; Robert Frantz, MD, Professor of Medicine and Director of the PH Clinic at the Mayo Clinic; and Nicholas Hill, MD, Professor and Chief of Pulmonary, Critical Care and Sleep Division at Tufts University School of Medicine.

**Dr Berman Rosenzweig:** It's my pleasure to host this roundtable for *Advances in Pulmonary Hypertension* with some key experts in PH joining me. Our focus today is to provide a roundup from the latest 6th World Symposium on Pulmonary Hypertension (WSPH) meeting that was held in Nice, France, in 2018. The intent is to provide some additional insight on the meeting to the PH community from key leaders in the field. I want to start with a brief introduction of our expert panel.

We are joined by Dr Val McLaughlin, who's a professor of medicine and director of the PH program at the University of Michigan in Ann Arbor; the esteemed Dr Greg Elliott, who is also a leading expert, and has been for many years in the field of PH, having served as chairman of the department of medicine at Intermountain Medical Center amongst many other leadership positions in the field; Dr Bob Frantz, who is representing the Mayo Clinic as Director of the PH Clinic at Mayo; and Dr Nick Hill, who's the Chief of Pulmonary, Critical Care and Sleep Division and professor at Tufts University School of Medicine. This is, in my opinion, an all-star lineup, with so many years of experience between you all. We are so fortunate to have you all here to hear your impressions of the last WSPH meeting in 2018.

**Dr Berman Rosenzweig:** Val, I wanted to start with you because you've had such a big role as a WSPH Steering Committee member for this meeting and previous meetings, and personally knowing how much work and effort you've put in to make it a success. Could you please give us a quick introduction of the main goals of the world meeting and what you think were the main highlights from the most recent world symposium?

**Dr McLaughlin:** Sure, well, thanks for having me, Erika. The world symposium was a tour de force, it was a collaborative effort from experts all over the world that span different disciplines from basic sciences to clinical care, from pathologists to cardiologists and pulmonologists; it was really a very special meeting. I think each time we have a symposium every 5 years, we want to not only highlight the new findings that have occurred in the prior 5 years, but dive deep into some areas and be provocative and I think that was the case at this particular meeting. I think the most provocative item that was discussed was the hemodynamic definition, and I imagine you're going to touch on that later, as well as some of the tweaks in the classification. I think one of my favorite things about this past meeting was the addition of the task force on the patient perspective. I think it's important not to lose sight of why we do this and to understand what the patients want. There were also important highlights in terms of the treatment algorithms and in terms of all the new genes that have been identified. I think one lesson that was most impactful in my practice is what came out of the genetics task force that Greg was on and how to apply all of the findings that we've had in genetics over the years to our patients. I've started to do a lot more referrals to genetic counselors and genetic testing since that symposium.

**Dr Berman Rosenzweig:** Yes, you've touched on so many important points and I'd like to hone in on some of them a little more. Provocative is a great word to describe the meeting, because I agree, and I'm sure other task force members would agree as well, that there were certain parts of the proceedings that have led to many further discussions since the WSPH meeting and I think that's part of the process and part of the goal, to generate discussions for the scientific community and for future meetings. I'd like to start specifically by asking the other panel members about their thoughts on the update to the hemodynamic definition with the proposed modification to define PH as when the mean pulmonary arterial pressure (mPAP) is greater than 20 mm Hg and the pulmonary vascular resistance (PVR) is greater than 3 Wood units. I'd like to get your thoughts about how that might impact clinical practice.

**Dr Elliott:** I'll start because then people can push back. I mean, I view the catheterization as a diagnostic test, maybe like a pulmonary function test, and I'm fine with accepting a definition built around what we know are normal pulmonary hemodynamics. I think the subtle issue for me is going to be knowing when to diagnose the disease, and I think the catheterization or the numbers that we pick, an mPAP greater than 20 mm Hg, obviously for me just doesn't translate to diagnosing disease in a patient. For me, that would be the key starting point on the new definition.

**Dr Frantz:** It's been really fascinating to me because I've had the opportunity

to be involved in a number of sessions about the new definition, debating about whether it should be incorporated. Right now I'm actually doing a Point/Counterpoint piece with Dr Brad Maron**,** which will be published in *Chest* relatively soon, about whether the new definition should be embraced in clinical practice, and I think you're spot on in terms of talking about hemodynamic catheterization as only one element of what goes into a diagnosis of pulmonary arterial hypertension (PAH). I think that part of the impetus was of course the goal of earlier diagnosis of PAH, although the majority of problems with early diagnosis do not have to do with the hemodynamic definition, they have to do with failure to think of the disease process and pursue testing to find it, as opposed to seeing a lot of patients who can meet this new definition that before were being ignored in some way. So I don't think that the goal of earlier diagnosis will be served in a broad context that well by the change in definition, although there will be some patients; and I think context is really everything. If a patient has scleroderma and you're doing a right-heart catheterization at 4:00 pm, and they have been fasting all day and they're on a diuretic with a wedge of 4 mm Hg, then they can easily have an mPAP of 22 or 24 and still have a PVR over 3 Wood units and very likely do have significant pulmonary vascular disease. On the other hand, there's opportunity for mischief here too, where there could be a fair number of patients who have borderline elevation of PVR and who have a lot of hypoxemic lung disease or have some tendency to heart failure with preserved ejection fraction with borderline wedge pressure, and that could easily be miscategorized because we don't really have a good nonbiopsy biomarker of the pulmonary vasculature to say that there is true Group 1 pathology. I do like the concept of calling attention to findings that are outside the bounds of normal, and I think that makes sense with an mPAP between 20 and 25 mm Hg, that that's really not normal. On the other hand, there are an awful lot of different situations that can result in that pressure and so if it's misapplied in clinical practice, it could cause a lot of mischief with overdiagnosis and psychological anxiety and all the rest of that for causing that kind of concern about PAH when maybe they don't really have PAH.

**Dr Hill:** I agree with what Greg stated about how the upper limit of normal doesn't necessarily define a disease. According to the Kovacs study, a meta-analysis on over 1000 catheterizations in healthy individuals that was published in *European Respiratory Journal* in 2009, the mPAP was 14 mm Hg and 2 standard deviations above that was 20 mm Hg; so I don't think we can argue that the definition of normal is fairly clearly established by that. The problem is, how do you define disease, and are there multiple diseases?

Another problem is that even though there are studies that have shown increased morbidity and mortality in that borderline group with mPAP of 21 to 24 mm Hg compared to patients with lower pulmonary arterial (PA) pressures—we don't understand the pathophysiology; there may be multiple things going on there, and it's really just an association at this point. We don't understand whether these people should be treated and whether they respond to any treatments, so we simply don't know enough, I think, about this group to change the definition at this point.

One other problem that is inherent in the definition that was proposed was picking the PVR of 3 Wood units. If the committee wanted to adhere to the same rationale for picking 20 mm Hg as the upper limit of normal for mPAP based on the Kovacs study, the average PVR in normals in that study was actually about 0.9 Wood units; 2 standard deviations above that and you get 1.66 Wood units, so 3 is quite a bit higher than that, and if you adhere to 3, you're going to have a hard time finding many people whose PVRs are 3 or greater who are alive, because the transpulmonary gradient becomes fairly narrow when you lower the definition like that, and the only way you get a PVR that high is to have people whose cardiac outputs are pretty low.

**Dr Frantz:** What I've seen that way, is you sometimes see underestimation of cardiac output. I've seen a couple of patients in the last year already who had a cardiac output that was estimated by indirect Fick, and that inadequate technique resulted in underestimation of cardiac output, overestimation of PVR, and the patients ended up on 2 different PAH therapies, felt no better, and clearly did not have the correct diagnosis, so it is certainly tricky in that way. I've also had patients who had a PVR that was borderline and I gave them nitric oxide and they completely normalized, and so we don't really think about giving nitric oxide to patients in that borderline category but if you do it, you'll find some that are actually just vasoconstricted and maybe that's a completely different problem as well.

**Dr Hill:** I was just going to say that because of the PVR problem, it's actually very hard to find patients who meet the criteria, and there was a pro/con in *European Respiratory Journal* in April earlier this year; I think Adam Torbicki was the first author of the con, and he pointed out that when they looked at patients from Hammersmith, in London, and also at his place in Poland, amounting to several thousand patients, only about 1% to 2% of the patients actually met this definition.

**Dr Frantz:** That's true. Dr Gerry Coghlan of Royal Free Hospital in London has done a nice subanalysis of the Detection of PAH in Systemic Sclerosis (DETECT) registry, and also demonstrated that patients who are borderline are only slightly more likely to end up meeting the classical criteria over the next 3 years than patients who were initially not so borderline, so I think, as a marker of patients that are going to go on to have PAH, it's also imperfect even in the scleroderma world.

**Dr Berman Rosenzweig:** Another great point. Val, do you want to chime in here, because I'm sure you have an opinion as well and we would like to hear your thoughts.

**Dr McLaughlin:** It's a great discussion. You guys are right. These patients are extraordinarily rare. In fact, just in the *European Respiratory Journal* in the past

month or two we published our series of patients that we have screened with scleroderma and we've done a lot of right-heart catheterizations. If you look at all of the right-heart catheterizations we've done for this over the past few years, you'll find one or two additional patients who would be diagnosed with that new definition. It's extraordinarily rare. But I think Nick made a good point about the PVR, and I wouldn't be surprised if that topic gets taken up at the next world symposium.

**Dr Hill:** I'm sure you're right.

**Dr Berman Rosenzweig:** These are great points. I wonder in terms of your clinical practices and research, between let's say now and when there may be further official discussions, if you come across one of these patients who falls into this hemodynamic range (mPAP 21 to 24 mm Hg, and PVR > 3 Wood units), would you just observe them, treat them, collect data, create research around this topic? What do you plan to do?

**Dr Frantz:** Well, I think, being fair to the guidelines, they do very clearly state that this new definition does not imply treatment of these patients in any specific way and so that's clear cut and well stated. On the other hand, the idea of exercise-induced PH kind of continues to fail to make the grade even though things that to me are just about as borderline as PVR of 3 are being incorporated. In my mind, if anything, I'm finding we're doing more exercising hemodynamics, and if you have somebody whose borderline PAP goes to 100 mm Hg with exercise, and the cardiac output response is impaired, then that patient very likely does have pulmonary vascular disease as opposed to others where the PVR actually falls and the PA pressure doesn't really go up, or the wedge shoots up and we really have heart failure with preserved ejection fraction. In my mind, I think we're being very careful to do super deep phenotyping with regard to vasoreactivity, exercise response, and understanding the phenotyping of these patients in a way that requires an expert center. It's just going to be much more difficult to do out in the routine clinical practice world.

**Dr Hill:** I think we need to study this group more carefully. I would get rid of the PVR greater than 3 Wood units requirement so that you can look at people whose mean PA pressures are greater than 20 mm Hg without that restriction. You'll get about 5 times, at least, as many patients, perhaps more, and they can be followed so that we can understand more about pathophysiology, about what's contributing to the increased mortality in this group.

**Dr Berman Rosenzweig:** This is really a great discussion and I'm certain it will continue on, and that by the next meeting we're also, as Val mentioned, continuing to debate and hopefully coming up with some additional modifications once we study this further. And to your point, Bob, about the exercise testing and what it means for exercise-induced PH certainly, that's still wide open for further study as well. I'm going to move on because I want to touch on another topic that I think is very important. I thought the addition of the phenotype of very robust, vasoreactive responsive patients into the diagnostic classification as a separate group in WSPH Group 1 was an important addition. All of you have many years of experience, and I'm sure have seen robust acute responders before, but it's surprising to me that those that who haven't seen as many WSPH Group 1 patients do not necessarily buy into this concept, and I just want to poll the group in terms of your impressions about the addition of that to the classification system, because I do think identifying these patients as having a different phenotype can be very important, not only for them but for awareness in the field. Does anybody want to respond to this addition?

**Dr McLaughlin:** Erika, I think it's a really valid point that this group is different; there's something different about them, whether they have more smooth muscle cell hypertrophy and vasoconstriction and less intimal proliferation, or they just have another abnormality, but they're a different group of patients. If they have that response, calcium channel blockers may be enough to have such a wonderful long term prognosis. I'm lucky if I see one or two of those a year in the referral practice that I have, but they're clearly different. I think my concern about the way the classification is done is, when do you put them in that classification or what if they lose responsiveness over time? Many of them, the true responders, don't lose responsiveness, but if they have that response at the time of their catheterization, you still need a trial period of calcium channel blockers to make sure they clinically respond, so there's some floating around of the actual nomenclature for an individual patient that we need to be cognizant of, but they're clearly a very different group.

**Dr Hill:** I agree. I think there are differences within the group, too. On one hand, you have the super responder patients that Val just alluded to, the ones we look for who are likely to be calcium channel blocker responders. I can recall one patient I saw years ago who started out with PA pressures of 100/40 mm Hg and in response to 5 ppm of nitric oxide, with every beat, the pressure came down and settled at 30/20 mm Hg over just a few minutes. I was concerned about removing the nitric oxide and the pressures went right back to 100/40 mm Hg going up with each beat. The patient didn't notice any difference at all, and she did very well on calcium channel blockers, not surprisingly.

On the other hand, another super responder I saw to epoprostenol was a woman who had similar pressures but was in florid right-heart failure, with a cardiac index of 1.5 L/min/$m^2$, and she went on 13 years, even though her prognostic factors would have said she should have lived less than 6 months at the time, and I know we've all seen these patients. She did not respond at all acutely, and yet her pressures virtually normalized, her mPAP dropped to 26 mm Hg, her PVR was well within normal limits and she died last year of a complication of another disease and not of PH, so that's another example of a super responder, not acutely vasoreactive, but obviously highly reactive to prostacyclins.

**Dr Frantz:** Nick, did you leave her on intravenous prostacyclins even though the PVRs had essentially normalized?

**Dr Hill:** Yes, I kept her on it.

**Dr Frantz:** I have a similar patient whom I met peripartum some years ago who was really in florid right-heart failure, not that acutely vasoreactive, and we treated with parenteral epoprostenol, and after several years when I did repeat catheterization, her PVR was flat-out normal and I thought, well, maybe she had a peripartum problem that's now gone. And so I actually weaned her off all of her PH therapy and she did all right for about a year and then that PA pressure started going back up again and I had to resume parenteral prostanoids**.** It was just crazy because we don't think of patients that are on parenteral prostenoids as having full normalization of PVR and so there was something about her that was very responsive to prostanoids in terms of being able to normalize PVR but did not maintain that with cessation of the therapy. I think at least identifying these kinds of unusual patients is valuable and maybe as we get better at metabolomics and genomics and proteomics, we'll be able to get signatures about those patients that tell us more about their disease state.

**Dr Elliott:** Erika, I've wanted to see this group identified and called out for a long time. The first one I had we tested with epoprostenol in the cath lab in 1984, and I'm happy to tell you she's still alive. And coming back to how we started our discussion, seeing a lot of this through the patient's eyes, when I met this young woman, she and her husband had been told she had a year to live. That was before the cath and acute vasoreactivity testing. They really are a unique group of patients; as I think Val mentioned earlier this year, we only see one or two of them a year if we're lucky but when you see it, it's different, and it's really important to call it out for the patient because it helps them to understand that they have a disease that's very often very treatable with a very good prognosis, unlike many of the other patients. So I was really glad to see it called out and of course, putting my genomics hat on for a minute, I've always talked about this as the vasoreactive phenotype with the idea that someday we'll figure out that genetic signature and really understand what this is all about, and maybe have, for better or worse, targeted therapy for it.

**Dr Berman Rosenzweig:** Yes, I couldn't agree more and that's why I think, even if it's a matter of working out some kinks as Val said, for example, with regard to if a patient subsequently becomes nonresponsive to acute vasodilator testing, what do you call them, the fact that they are identified as a separate group underscores what everybody on the panel has said, that if you've managed one of these patients, it's quite rewarding, because they can be so responsive to therapy. So personally, I was also glad to see them highlighted there and hope there will be more work done to identify, as you said, Greg, whether there is a particular genotype that's associated with robust responsiveness.

With that, I'd like to focus a little on the Genetic Task Force, which was a real highlight of the meetings. There has been a lot of exciting recent movement in the identification of other genes related to PH in both the adult and pediatric world, and I'd like everybody's thoughts in terms of how that might impact your clinical practices. Specifically, I'd say that we all probably have patients that we've seen for many years and we may have done genetic testing when we first met them, but I think there's an opportunity to resend genetic testing on many of these patients now. Is that what you're all doing and maybe you can share some of your thoughts on that?

**Dr Elliott:** I'll jump in and congratulate Val. Val took it home and Val's team is now doing the genetic testing and counseling, had a poster at PHPN that shows their work and I just thought it was fantastic.

**Dr McLaughlin:** Yes, thanks. I learned so much and I was able to practically apply it in our practice. Another point is the issue with pulmonary veno-occlusive disease (PVOD): when you're suspecting it, that *EIF2AK4* testing can be sent. We are doing that and we have found it very helpful, but I think another thing to emphasize is just the importance of the genetic counselor in this. I don't feel qualified to do that myself and those folks are really fantastic and make great contributions; they are an important part of our health care team now.

**Dr Elliott:** That's a wonderful point Val, absolutely wonderful.

**Dr Berman Rosenzweig:** Yes. Any other thoughts on this?

**Dr Elliott:** I would add about the *EIF2AK4*, just a point, and that is, when we've looked at this, and we've looked at it, our European colleagues have looked at it, the *EIF2AK4* mutation has also been found in very small numbers of patients diagnosed with classic Group 1 PAH, and so sometimes I think, even if you're not suspecting PVOD, you have to realize they may actually have heritable PVOD–pulmonary capillary hemangiomatosis and look like PAH.

**Dr Berman Rosenzweig:** That's really important. I think it was also highlighted, in terms of being a spectrum of disease now, that you can have features of PVOD, pulmonary capillary hemangiomatosis, and PAH. My one quick question is about the turnover and being able to get these genetic results quickly. So if you have a patient and you suspect PVOD, and they may be quite sick, and you're trying to determine whether you might list them for lung transplant, how quickly in the real world setting can you turn over these genetic results for the clinician?

**Dr Elliott:** I don't know that I've ever done one as a rush, I think that's one of the problems. I can't actually tell you the shortest time window that we could turn it around in our lab, but to have a result in a couple of weeks with the targeted gene panel would not be unusual.

**Dr McLaughlin:** I just want to say one of the things that we sometimes run into is just the insurance coverage, and then the cost if the insurance doesn't cover it.

**Dr Berman Rosenzweig:** Yes, that's an issue and of course, access for other smaller community hospitals and being able to do this from a practical standpoint, is definitely something that I hope folks will be working on in the near future, so that one could really translate this into clinical practice. Unfortunately, in the absence of a lung biopsy sometimes we're relying on explanted lungs to confirm the diagnosis if we highly suspect it, but the genetic testing could potentially turn into a clinical diagnostic tool. That's the hope for the future, so hopefully we can broaden and improve upon how this is put into clinical practice because it really can make the difference to the patient.

**Dr Elliott:** If I may add, even the 2015 European Respiratory Society/European Society of Cardiology guidelines pointed out that testing the *EIF2AK4* and finding pathogenic mutations is diagnostic. One doesn't need histopathology if you find that. When you don't have a critical patient and you suspect PVOD with PH, you don't need to do a lung biopsy. It obviously subjects them to mortality risk. Our own experience here—I figured it out one time and I actually looked at the cost at Intermountain of the lung biopsy that we had done compared to the genomic test, and we saved several thousand dollars by doing the genomic test over the lung biopsy.

**Dr Berman Rosenzweig:** That's a great point. One final focus here. Val mentioned the newly developed task force on patient perspective. I want to, first of all, commend you and your team for focusing on the patient perspective, because as you said, this is obviously the critical core of all that we do, and so I want to get the group's impressions on that as an addition to the last meeting, and hopes for the future with regard to patient input on future proceedings and meetings.

**Dr Elliott:** Once again I'll jump in and say hats off to Val and the organizing committee. Not only was it a terrific idea to include the patient perspective, which we all know often differs from the doctor's perspective or that of the medical professionals, but they also picked a terrific chair for that, Mike McGoon, and I thought Mike did an outstanding job.

**Dr Berman Rosenzweig:** Great, absolutely agree Greg.

**Dr McLaughlin:** Yes, I also agree. One thing I heard from them was that they really want to hear about palliative care at an earlier stage, and I personally have a challenge talking about that, especially earlier in the course of disease, because so many patients come to us for hope and we spend so much time doing everything we can. I tend to wait until I know I've exhausted my options and they're not a transplant candidate to bring up the concept of palliative care but it seems to me that they wanted to hear about it a little bit sooner.

**Dr Berman Rosenzweig:** That's a great point. I agree. I think that we are often faced with patients who've been told, at least in the early years, there are no options and we have always focused on providing options and hope for them. I think it's a little harder for some of us, at least for me, to introduce early on, but it was definitely a highlight of that task force.

**Dr Hill:** I think it really depends on how palliative care gets presented to patients. I've always thought that when we take care of patients with any chronic illness, we should be thinking along palliative care lines. We don't have cures for diseases like PAH and so the focus really needs to be on symptoms. Certainly we would like to extend survival as much as possible, but to help them get the most out of the life they have, that's really the focus of palliative care, and I think when presented from that perspective, that we're trying to enhance function and quality of life with palliative care, I think it's a nice, easier sell.

**Dr Frantz:** Nick, I think that's exactly right, that we try to take more of a parallel approach, where we say we're going to do everything that we have in our power, to the extent that you wish to do so, to treat your PH effectively; but there's another team that has much more expertise than we do about symptom management and the psychology of dealing with chronic disease and uncertainty, and we're going to take a parallel track where we're going to be holistic, and we're going to push forward with everything we know how to do medically, but here's another team, that's also part of *your* team, that will help you to deal with both side effects and issues that come up from a psychologic and adaptation perspective. With that, I think we've been able to make some inroads into helping patients see palliative care a little bit sooner and hopefully gaining from that. We started to incorporate quality-of-life instruments into our clinical practice now, in a way where we're doing the PAH Symptoms and Impact (SYMPACT) as a 1-day patient-reported outcome for patients coming to the clinic and trying to use that. Actually, my colleague Dr Hilary DuBrock has developed a research project of referring patients whose SYMPACT scores are high to palliative care or not in a randomized way, unless the clinician feels they absolutely need to see them, and to try to see whether that earlier referral based on SYMPACT scores might actually contribute to better quality of life and better patient adaptation to the disease. So I think this whole field of the patient-reported outcome and palliative care and patient-centered care is really critically important and moving faster than it has in many years.

**Dr Berman Rosenzweig:** Thank you. I think those are all terrific and insightful comments and I couldn't agree more that this is very important to the patients and families and we can all learn more—at least, certainly I can, as a practitioner, to implement this earlier on for patients. We're winding down, but I do want to take a moment to focus on your work, Val. You recently, with others, established an association for the next, and future, World Symposium on PH meetings called the WSPHA. I wanted to give you an opportunity to share the plans for that, and the goals of the WSPHA in terms of planning in between these WSPH meetings and to

share those with the community, if you don't mind.

**Dr McLaughlin:** Sure, thanks for giving me the opportunity to talk about that, Erika. Essentially, the leaders of the last world symposium looked at each other afterwards and said, "That was really interesting, there was a lot going on, I wish we would have had more time to think about this, or more time for interaction between this group and that group, or more continuity." So we decided to form this association that really, I hope, is going to help the every-5-year symposiums go on in perpetuity and have more continuity. We've already had a couple of meetings. We formed a large and what I believe is a very inclusive scientific committee that has broad representation, and we're starting to brainstorm some of the things that we think should be incorporated into the next meeting, forming some subcommittees to explore whether this idea is going to have enough data to discuss or whether we should be going in that direction. The increase in communication and planning is going to make the next meeting in 2023 even more rigorous, and maybe even more provocative. It's really been a pleasure to be a part of that and to be able to work with so many different folks who are being very thoughtful about the future of PH. I believe it will allow for more crosstalk between the committees. When you start planning this just a year or two in advance, the committees are all working hard and they're getting their work done, but sometimes you get there and they haven't shared some of their ideas with each other, and it makes it more of a challenge. This will be a really nice opportunity to have a little bit more thought going into some of the topics and a little bit more communication amongst the different task forces in between meetings.

**Dr Berman Rosenzweig:** Thank you, Val, I think that this is very exciting for everybody on the call and in the community, particularly regarding some of the questions that have been raised, and some of the thought-provoking areas of interest which can now be focused on in between meetings. I believe these discussions are so valuable in terms of planning ahead for the next WSPH and prompting research to answer some of these important questions.

It was an honor to lead this discussion and hear your insights. On behalf of the PHA and the *Advances* editorial board, I want to thank you all for your incredible wisdom and thoughts on the 6th WSPH meeting.