Cure HHT drives science forward through government advocacy, seed grants and other means. Turning your donations…

into millions of dollars dedicated to funding new treatments, advancing diagnostic technology, and developing new drugs.

From 60 attendees at our 1st International Scientific Conference in 1996 to nearly 300 at our 2022 meeting in Portugal, we have helped grow the number of dedicated and compassionate clinicians and scientists who are keeping us on the cutting edge.

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www.curehht.org | hhtinfo@curehht.org
P.O. Box 329, Monkton, MD 21111
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On the Cutting Edge

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Cure HHT has invested $2M in seed grants for research, which have been leveraged to $51M in funding (*a nearly 2,450% ROI)* from the DOD, CDC, FDA & NIH for researchers and clinicians.

**Drs. Al-Samkari, Hetts and Hughes have all previously received seed grants from Cure HHT.*

THE CUTTING EDGE OF SCREENING

Steven Hetts, MD

Chief of Interventional Neuroradiology at the UCSF Mission Bay Hospitals
Co-Director, HHT Center of Excellence

How is Dr. Hetts keeping us on the cutting edge?

Dr. Hetts and the team at UCSF received a grant from the Department of Defense for its study dubbed "project Aviator." **One of the study's goals is to develop a singular MRI scan that would look for any AVMs in the brain, lung, or liver.** This would potentially eliminate the current need for separate imaging on the brain (MRI), lung (echo bubble or chest CT) and liver (ultrasound). This one scan would take less than 45 minutes!

THE CUTTING EDGE OF DRUG DEVELOPMENT

How is Professor Hughes keeping us on the cutting edge?

In his lab, Professor Hughes is creating real, living AVMs on chips. **"Basically, we can create an HHT patient on a plate the size of an iPhone," says Hughes.** This is being used to find drugs that will turn AVMs back to normal vessels or stop the AVMs from forming altogether. The drug Pazopanib, which will soon launch a clinical trial, was proven effective on the chip platform.

> ***Everyone I've met who focuses on this disease feels a strong sense of commitment to helping the patient. We all feel very called to help. I want them to know that.***

THE CUTTING EDGE OF THERAPEUTICS

> ***Cure HHT is an indispensable catalyst for scientific breakthroughs. Without Cure HHT, I shudder to think what the landscape for this disease would look like. Things would be very challenging. Cure HHT helps create a lot of hope, and is a true partner for scientific change.***

Hanny Al-Samkari, MD

Hematologist, Massachusetts General Hospital & Harvard Medical School
Associate Director, HHT Center of Excellence

How is Dr. Al-Samkari keeping us on the cutting edge?

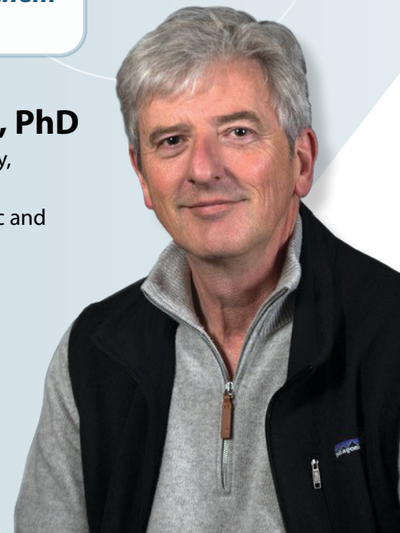
Dr. Al-Samkari has played pivotal roles in the ongoing PATH trial, the soon-to-launch PAZ trial, and the upcoming VADERIS trial – which will be the first pharmaceutical-company sponsored drug trial in this disease. On the importance a successful clinical trial would have on future HHT treatments: **"One success catalyzes so much more…ultimately, what we want for patients is a plethora of therapeutics and medicines and options because every patient is different."**

Christopher C. W. Hughes, PhD

Dept. Molecular Biology and Biochemistry, University of California – Irvine

Chair, Cure HHT North American Scientific and Medical Advisory Council

Cure HHT Basic and Translational Science Research Director



To read the complete interviews, visit: www.curehht.org/cuttingedge

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CHRIS HUGHES

On the Cutting Edge

On the current state of HHT innovation

Q: Can you tell us about your professional background and how you first got interested in HHT research?

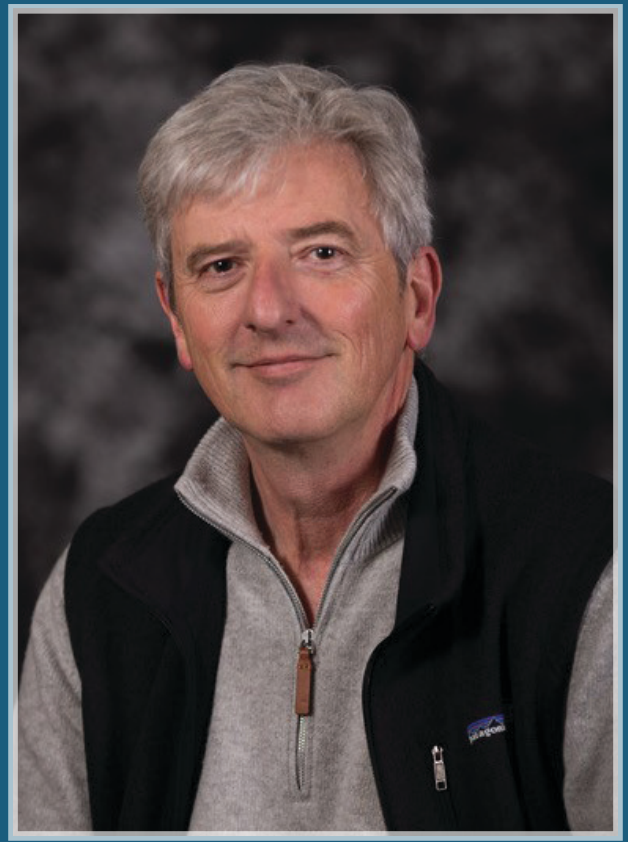
A: I have my Ph.D. in vascular biology from the University of London. When I first moved to the U.S. in 1988, I started working at Harvard and then Yale in vascular biology. I ended up starting my own lab in 1996 at University of California – Irvine and worked on various aspects of blood vessel development. At some point – probably 15 to 20 years ago by now – I saw a call that Cure HHT had a request for applications for a grant. At the time, I had a particular theory about what might be going wrong in HHT, so I applied and got funding. Part of the deal with the funding is you do the work, and then you go to the following year's annual meeting – the patient and physician conference -- and present your findings. So, I went to the meeting in St. Louis around 2007. They had a GRMAB (Global Research and Medical Advisory Board) meeting afterwards and Marianne asked me if I wanted to sit in. I said, "Yeah sure." At one point, I put up my hand and asked if were OK if I spoke. They said absolutely. I guess I said some stuff that seemed to have an impact. The next thing I know, I'm chairing the committee to come up with research directions for HHT. And that's very much what happens with Marianne. She has a very strong gravitational field. If you get too close, you just can't get away! She's just so wonderful. So, that's what happened. I started working with Cure HHT and I just haven't left. There are such wonderful people involved here – the staff, Marianne, and I'm always meeting patients which is great. That's how it started.

Q: From when you first started getting involved in HHT research in 2007 to today, how have you seen the field change?

A: Well, for one, there's a lot more work being done in HHT. And a lot of that is thanks to Marianne and the foundation and the work they've done to create that -- and get funding from bodies like the National Institutes of Health. The annual meetings have really brought in a lot of researchers over the years to focus on this disease. Cure HHT has been a big part of growing the community and generating interesting research. In recent years, we've had a lot of important model systems developed that have really helped – such as genetic studies with Zebrafish, mouse models and more – that have really helped our knowledge. We're just so much farther along today.

Q: Can you tell the HHT community more about your work in developing AVMs on chips, and how this can help with future drug development?

A: Sure. But first, a quick step back. It's important to know that what happens in HHT is improper connections between arteries and veins. The arteries are the ones carrying oxygenated blood around your body and the vein carries deoxygenated blood back to your lungs. In your tissues, the oxygen is given up to the tissues that use it through small vessels called the



Christopher C. W. Hughes, PhD

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* ***Cure HHT seed grant recipient***

capillaries, which connect the arteries and veins. What happens in HHT is you get malformations and improper connections between arteries and veins. That's basically what HHT is. So, what we have we're doing in our lab is creating arteries and veins on a chip. We can either connect them with normal vessels or connect them with AVMs. So basically, we can recreate an HHT patient on a chip. This device is the size of an iPhone, and we can put 16 AVMs – living, real AVMs – on this plate. We can then use that for drug screening and trying to find drugs that will turn the AVMs back to normal vessels or to stop the AVMs from forming in the first place. It gives us a way to test new drugs without patient involvement. If they work, we can move on to patients. The PAZ trial – we've shown that that drug works on our platform. We can block AVM formations with PAZ, and we're seeing that drug is working for patients. Now, we're looking for other drugs that can work on our platform that will also work for patients. So, we're using it as a way to screen drugs.

Q: That's truly incredible work. What are some of the next steps?

A: Two areas. A senior post-doc in my lab currently – Jennifer Fang – is about to start her own lab at Tulane. She's been doing the work in our lab, but we're going to be going in two directions with this; One is to use these AVMs to develop a mechanistic understanding of what happens in these regions and asking: "Why do these blood vessels go wrong?" So, we have some data on that and some ideas on that. Jennifer is going to follow up on that. I'm going to focus more on drug discovery and how to fix these vessels. Those are the two direction our labs are going to go in.

Q: What do you find rewarding, whether personally or professionally, about focusing on HHT.

A: It's the patients. Marianne often has me come to patient conferences and help explain the science to the patients, and I love the chance to interact with patients and try to answer their questions. That's the rewarding part. But I tell this story: several years ago, I came home from work and my young daughter is 9 or 10 at the time. She says hello and asks me how was my day. I tell her; "Oh, it was great". She then asks: "Did you cure anyone?" She knows I do lab research and so I said: "Well, no that's not what I do, right? I do basic research. The work I do, in 20 years' time may help patients." I could see the disappointment on her face that I wasn't actually helping patients. That made me think I wanted to do more translational research and get closer to the "pointy end". That actually coincided with when I first started getting involved with HHT. So, my whole research program now is much more translational than it used to be. I like the idea of coming home and telling my daughter; Yes, I did help patients today. We did get to that point, actually. The first clinical trial of PAZ, I was one of the people who helped design that and was an author on the paper that showed yes, this could help patients. Now lots of patients get PAZ and love it. I was able to say to my daughter, actually yes. I did do a study that helped patients.

Q: What would your message be to patients about the state of research today?

A: For many years, we've been fumbling around in the dark trying to figure out ways to help patients. In the last 10 years, the pace of discovery and understanding has just accelerated so much that we've entered the phase of having new treatments to help patients. PAZ is a great example. We're not all the way there. We don't know if we can target large AVMS, but we're certainly helping pervasive bleeding. We're going to have new drugs coming along faster and faster. I'm really optimistic that we're making major strides right now.

Q: If I gave you a crystal ball, what do you hope you'd see in 5-10 years' time in HHT research or treatment?

A: We'll, what everyone wants is a cure. What I imagine a lot of patients don't know is that we know exactly how to do that. We do. HHT is relatively simple disease, we think. It's a lack of a cell surface receptor – ALK1 or endoglin. And we know how to put those genes back in to cells by gene therapy. What's holding us back is the availability of a safe delivery system. We know if we put in a good copy of ALK 1 into endothelial cells of patients, they will not get HHT. The problem is, how do you get that gene into the cell reliably and safely? That's not what HHT researchers do. That's what gene therapists do. We are all waiting for the gene therapy people to figure out how to safely deliver genes to cells. We're getting there. There are some examples of people who have done that successfully in trials in other diseases. So, I would think there's a reasonable chance that in 10 years, there could be a form of gene therapy for patients. That would be my hope. Whether it happens, unfortunately, that's outside my scope.

A: Community is the first thing. Cure HHT gives us a place to collaborate with everyone who is working on this disease. We get together and share ideas on a regular basis, and that's really important – and it happens because of Cure HHT. I've said to people many times: I don't think I've ever had a good idea sitting in a room alone. But I've had a lot of good ideas sitting in a room talking to people about science. That back and forth is what gets creative juices flowing. Science moves forward that way. A big issue with basic science is access to clinicians and talking through what they and patients need. I've got the science down. But what's the clinical side say? Cure HHT bridges that gap. And they also help with sources of funding and bringing new people into focusing on this disease.

But also, here's a great example; there was a time where I wanted to create stem cells. That would usually take months and months and months to get samples from patients. Not with Cure HHT. I called up Marianne, told her what I needed. She asked me how many patient samples I needed and when? Two days later, she got me the samples and we're off to the races. It was unbelievable. Just having a resource like that is unbelievable.

Q: Thank you so much for the time, Chris. Is there anything else you'd want to share with the patient community?

A: I would just want them to know that everyone I've met who focuses on this diseases feels a strong sense of commitment to helping the patient. We've met so many of them. And that's the coolest thing about Cure HHT is they bring together researchers, clinicians and patients. We all feel very called to help. For example, I do a lot of work on cancer as well – but I'm hardly ever meeting cancer patients. I meet HHT patients all the time. We all feel a strong level of commitment to help patients. I want them to know that. Oh, and that you need to wrap Marianne in bubble wrap and keep her safe! We couldn't do any of this without her.

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STEVEN HETTS

On the Cutting Edge

On the current state of HHT innovation

Q: To start, some congratulations are in order! Your Aviator project recently received a grant through Department of Defense - and specifically, you were the only awardee in the category of vascular malformations. Can you tell the community more about Aviator?

A: Yes, we were very fortunate to get funding support. As for some background, at UCSF we're lucky to work with really outstanding MRI scientists. David Saloner is a PhD in our department who is one of the pioneers in developing MR angiography – noninvasive images of the blood vessels. What he and others have learned over the years is that sometimes we can use a different kind of contrast agent that can provide beautiful MRI images.

The way we've constructed this study, there are three specific aims:
The first is to develop one MRI that would scan from the top of the head to the bottom of the liver and look for any AVMs in the brain, lungs, or liver. This would be instead of having to get a separate brain MRI, and a lung echo bubble or chest CT for lung AVMs, and a liver ultrasound or MRI. This is a single exam for all three organs. Ideally, this would take under an hour. That's the goal. If we're successful, this type of screening exam could then be done on a regular MRI machine available at most hospitals.

The second goal is to do more of a deep dive on people who have pulmonary and liver AVMs and do what's called quantitative MRI flow imaging of the heart, lungs, and liver. This would help us see precisely how much flow is going through those AVMs, which would help us better understand how AVMs change over time in response to therapies. For liver AVMs, for example, there's not a good solution to embolize them. Some people who have heart failure related to high-flow liver AVMs are put on Avastin – a cancer medication that causes blood vessels to regress. We've seen that we can actually reverse heart failure this way. One way to measure that quantitatively is to measure that with a flow scan. And we could do similar things with pulmonary AVMs before and after embolization.

The third aim is to do very high-resolution MRI scans of the brain to look at brain AVMs more precisely. Here, we are one of a very few research institutions around the world that have a very strong MRI magnet. It's a 7-tesla magnet. This higher magnetic field enables us to see very small structures. Our goal is to visualize brain AVMs in as much detail as we can in a catheter angiography. The hope is that we can develop a noninvasive MRI to get the same answers only available today through invasive techniques.

Q: That's tremendous! It may sound obvious given your previous response, but what should the patient know on how this trial may ultimately benefit them?

A: First, I must say; Whenever you're developing new

Steven Hetts, MD

Chief of Interventional Neuroradiology at the UCSF Mission Bay Hospitals

Co-Director, HHT Center of Excellence

* ***Cure HHT seed grant recipient***

techniques, we try not to oversell it. The real benefit is for the future. We need to analyze data and prove these are beneficial techniques that improve upon what we currently have. In the immediate term, the trial will help people learn more about their AVMs and what they are doing. But in the longer term, much more systematically, it could allow patients to not have four types of imaging studies for the brain, lung and liver and instead just go for one.

We're hoping to enroll 162 patients with HHT – so we'll need to recruit from well outside of our region here at UCSF. We'll need all kinds of folks – those with and without AVMs in the brain, lung, and liver. Anyone with HHT would be able to help this study.

Q: There's a lot of promising studies and trials underway or just beginning in HHT. I'm curious, if you had a crystal ball… what are you hopeful to see in HHT care in 5 to 10 years?

A: It's fun being at the University of California because there are some really forward-thinking people here. One faculty member is Jennifer Doudna, who recently won the Nobel Prize for CRISPR – which is a genetic editing technique. There are now some early clinical trials in sickle cell disease, as one example. This is basically a technique to genetically cure disease. HHT is not the very first one that this is headed for -- because we can do a fairly good job of managing HHT today. But also, HHT involves multiple genes – it's not just one. That's why sickle cell and similar diseases are the starting place. However, I think within the next decade it's realistic to have HHT gene therapy trials up and running. There's benefit to that timeline, too. By then, we'll have learned a lot from the first gene therapy trials in other diseases. It's a good place to be not the first condition targeted, but in the next cohort where we learn some and can design the trials a bit more safely and efficiently – but not far enough out where we're waiting 30 years.

Q: What do you think the biggest difference is in HHT care today versus when you first started seeing patients?

A: Honestly, I would say awareness is the biggest difference. When I first started in interventional neuroradiology, we treated many patients with brain AVMs. But we weren't systematically looking for HHT. Now, because we have a robust HHT center and we work with colleagues across various disciplines, the first question we ask today after someone is diagnosed with a brain AVM is: Well, do they have nosebleeds? Increased awareness has been the most important thing. It helps us provide care for more people, get them screened early, and treated properly. There's just so much more recognition today.

Q: How does an organization like Cure HHT help you as a clinician?

A: Very much, is the short answer. At the most basic level, helping to educate clinicians is a big one. We learn a lot from Cure HHT on how to better care for this disease. But they also help tremendously in patient referral. And the patients we're seeing are more and more educated and informed – which Cure HHT helps with. Research support really is invaluable. Cure HHT is outstanding at advocacy, and they've been able to encourage national spending and grants for HHT – like the HRSA grant for CoEs or helping secure the Aviator funding. Those sorts of advocacy efforts to support research are tremendously important in helping to make medical advancements.

Q: OK, last one: If you had one message for the HHT community, what would it be?

A: I'd want to reinforce the importance of getting tested early. It's just so critical. If you have a history of this disease in your family, genetic testing at birth is key. We need as many people as possible tested and scanned early. That way, if you have it, you can go through the proper scanning and be treated to avoid life-threatening complications.

Just recently, we've been treating a patient at UCSF shortly after birth. This patient has a very large vascular malformation in the brain. They had prenatal screening, and it was seen on those scans. So, we knew there was a vascular malformation in utero. We were able to treat shortly after birth and got the child out of heart failure and hopefully prevent hemorrhage in the future. So, my message would be on behalf of the youngest of patients: Get tested early.

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HANNY AL-SAMKARI

On the Cutting Edge

On the current state of HHT innovation

Q: How did you first get involved with treating HHT – and how did your professional interest in studying and treating the disease grow?

A: It was organic. As a resident in internal medicine, I had seen a few HHT patients. But I was still under the impression that this was a really, really rare disease. When I started as a fellow in hematology/oncology at Mass General, I started seeing tons of HHT patients. I thought; "My gosh, there are a couple hundred hemophilia centers in the country -- and I have far more HHT patients than hemophilia patients." I wondered if it was selection bias because we are an HHT center at Mass General, so are we just naturally seeing more patients? Then I realized, no – HHT is twice as common as hemophilia. It really demonstrated to me that the medical community hasn't paid attention like they should have.

I thought: Here are these patients that have this frequently awful disease, and it was clear that there was a lot of potential good I could do if I focused on HHT. It was inspiring to me. But what keeps me going is you never get tired of a patient telling you that all their life, before they met you, they didn't have a doctor who really understood the disease. We have the chance to really turn these patients' lives around.

Q: In addition to the ability to truly impact patients, what do you find most rewarding in your work with HHT?

A: Well, you said it. The No. 1 thing is always the impact on patients. But No.2, it's fascinating science. And I do think that's important for patients to know. HHT is an attractive area for physicians and scientists to enter. It's the sort of area that is both interesting and recent developments make it a fertile ground for someone to really make a major impact. Physicians and scientists want to make an impact. They want to do something that will really improve the lives of people. In many ways, focusing on HHT gives physicians and scientists a real ability to make a mark. It would be a shame to let that opportunity pass you by. It's a shame that so many others have over the last few decades. It's something we owe patients to remedy.

Q: You've played a critical role in the ongoing PATH trial, and in the upcoming PAZ trial. What do patients need to know about these trials?

A: I take care of a lot of rare hematologic diseases. For you to have advancements in your disease, you must have interest from investigators and academics – and from the pharmaceutical industry. You must either have something that looks very promising for future success or evidence of past success. One success catalyzes so much more. I joke that some of these really rare blood diseases have more drugs now than they have patients – and a decade or two ago, they had nothing. Once you have one success, that often spurs various corners of drug development from the academic side to the industry side to say – look,

Hanny Al-Samkari, MD

Hematologist, Massachusetts General Hospital & Harvard Medical School

Associate Director, HHT Center of Excellence

* ***Cure HHT seed grant recipient***

we can be successful here. In that case, the ultimate beneficiary is the patient.

So, given this, what I would say is: When you see a clinical trial as a patient, recognize that these trials are happening because there is a massive body of evidence before the trial even starts that makes these very promising potential therapies. By volunteering for a clinical trial, you have the opportunity to potentially derive great benefit yourself and also advance the science in HHT, which will ultimately help others. And also consider that even just one successful trial would likely lead to more developments and breakthroughs.

Q: In addition to PATH and PAZ, VADERIS is in the early stages of an upcoming trial for a promising HHT-related drug. Is there anything the community should know about the VADERIS trial at this stage?

A: It is early, but the drug is very promising. This will be the first pharmaceutical company-sponsored drug trial in this disease. That is a huge milestone. If this trial is successful, there will be more interest from pharmaceutical companies, which again will translate to benefit to patients. Ultimately, what we want for patients is a plethora of therapeutics and medicines and options because every patient is different.

Q: What does it take to create true breakthroughs within a rare disease -- and what gives you hope we're nearing that place for HHT?

A: The first thing it takes is a scientific understanding of the underlying pathology of the disease. Up until the last couple decades, we didn't really have that for HHT. Today, we have a much better understanding. We're in a place now where basic science can advance in parallel with the clinical science. We also have promising trials and enough patients to volunteer for those promising trials. I hear a lot of patients tell me after a trial; "Gosh, I wish my mother or grandfather could have had access to this." They'll ask me why this wasn't possible 20 years ago. I tell them the reason is because the science has advanced so much in the last couple decades. But in addition to science, you need funding – and that can come from the Department of Defense (DoD) and other national funding sources. But it's important to understand that for major trials, it takes a lot of money. It's important that people in the National Institute of Health and DoD have an understanding that HHT is a major problem and is a neglected disease and worth their time. Cure HHT does a great job of advocating on that behalf. These studies would not be possible -- and may not have been funded -- without Cure HHT's efforts.

Q: Well, thank you for that. As a clinician, how does an organization like Cure HHT help you?

A: Cure HHT is an incredible example of an effective advocacy organization. It has, over time, cultivated real and meaningful relationships with physicians, investigators, and scientists that have endured and created real impact. Cure HHT has made it very clear that it means business. The foundation has funded grants for studies. They have funded young investigator awards to enable them to go to conferences and present research. That makes a real difference. Cure HHT brings people into the field and gets them interested in this disease. The foundation has created real collaborations between clinicians and scientists. And those collaborations, ultimately, have led us to the breakthroughs we've had so far – and will certainly lead to more.

Cure HHT very much is an indispensable catalyst for scientific breakthroughs. Without Cure HHT, I shudder to think what the landscape for this disease would look like. Without the involvement of Cure HHT, things would be very challenging. They help create a lot of hope and are a true partner for scientific change.

Q: OK – last one for you; If you had one message for the HHT community, what would it be?

A: Be hopeful. For several reasons. No. 1, and I know this can be very person dependent, but things now are clearly better than they were a decade ago in terms of our options to treat patients. And things a decade from now, that jump will be even bigger. I know so many of my patients have told me they've watched their parents and grandparents suffer from this disease. They tell me they just want to avoid that for themselves and for their children.

Where we are, I am confident that the present is better than the past…and the future will be that much better. People who are suffering with this disease – have hope.