**Transcript (part 3 of 4)**

**Externally-Led Patient-Focused Drug Development Meeting on TSC and LAM**

June 21, 2017

tsalliance.org/pfdd

**Afternoon Session, Panel 1: Living with TSC and LAM**

**Steve Roberds:** Excuse me. Welcome back. For those of you who were here in the in the morning, I hope you'll agree it was a very impressive session to listen to the discussion of all of those in in the panel and out there in the crowd and all of your input and we're set for another similar approach in the afternoon, and I think it would be just as exciting and rewarding, taking a slightly different look at things.

So if you don't know me, I'm Steve Roberds. I'm the Chief Scientific Officer at the TS Alliance, which is a national nonprofit organization dedicated to finding a cure for TSC while improving the lives of those affected. It's my pleasure to welcome you to the afternoon session of this Externally-Led Patient-Focused Drug Development meeting on TSC and LAM. In the morning session, TS Alliance President and CEO Kari Rosbeck shared the clinical development pipeline for TSC and LAM.

I'd like to take just a moment to share a few highlights of a survey that was conducted just prior to this meeting. Early during the planning for today's Patient-Focused Drug Development meeting, we realized it was important to share with the FDA the big picture of TSC and LAM to put some numbers behind the impactful stories that you will hear today. As you've heard from this morning, these disorders are highly variable from person to person, so as you hear the stories, you may think to yourself, how generalizable is this experience? Is that story common, or is it unusual? So we will include in the Voice of the Patient report a thorough analysis of those survey data, but for today we included in the meeting booklet that you have just a few graphs summarizing some of the results that I'll just describe really quickly.

So to this survey, which was distributed internationally, we received responses from caregivers of children or dependent adults with TSC and/or LAM or from independent adults with TSC and or LAM. The survey was developed through extensive conversations with individuals affected by TSC or LAM, including some of today's panelists, and its format mimics the Patient-Focused Drug Development questions that we'll be discussing today. The most common manifestations overall include epilepsy, skin problems, developmental delay and other TSC-Associated Neuropsychiatric Disorders, brain tumors, and kidney tumors. The most impactful for children and adults and dependent adults are clearly epilepsy and TSC-Associated Neuropsychiatric Disorders. The scenario changes considerably when we look at how TSC and LAM affect adults. For those with TSC, kidney problems caused the most impact to daily living, followed closely by anxiety or depression and lung issues. Epilepsy, of course, is still very impactful, but remember, this survey was answered by people who can answer for themselves, so many of those who cannot answer for themselves as adults mean they were probably severely impacted by epilepsy, cognitive impairment, and social or behavioral issues, as well. For those with LAM, not surprisingly, lung issues topped the list, but anxiety or depression is second, and I think you'll hear some specific examples of that today, followed by sleep problems, kidney issues, and lymphatic issues.

The variability of TSC and LAM led to our decision to split this day into two different sessions, as the impact of the disorders and the relative risk profiles can be different between infancy or childhood and adulthood. This afternoon, we're focusing on tumor burden and LAM, as these are especially impactful as individuals get older. We deeply appreciate the participation of the community: patients, the caregivers, the relatives. Many of today's topics may be difficult to talk about in an open setting, but it's very important that your voice can be heard to impact future drug development to provide a perspective on how our FDA colleagues intend to use the patient voice to evaluate development programs and drug applications.

It's my honor to introduce Dr. Martha Donoghue. She's a team leader for the gastrointestinal cancers team in the Division of Oncology Projects 2 in the Office of Hematology and Oncology Products in CDER at the FDA. Dr. Donoghue provides regulatory oversight, engages in clinical review activities, and advises stakeholders involved in the development of drugs and therapeutic biologics for the diagnosis, prevention, and treatment of cancer and related disorders. Please welcome Dr. Donoghue.

**Martha Donoghue:** Well, good afternoon, and I'd like to extend my sincere thanks to the Tuberous Sclerosis Alliance and The Lymphangioleiomyomatosis Foundation (now I'm going to say "LAM" but I just had to try it!) for hosting this Patient-Focused Drug Development meeting, and of course a very sincere thank you to patients, caregivers, and other stakeholders for participating in this meeting. Of course, I think the main reason we're here today is to work together to move drug development forward, so that there are new safe and effective treatments for patients with TSC and LAM available in the not-too-distant future. We all recognize that new treatments are needed and the sooner the better. To date, my office, the office I work in at the FDA, which is the Office of Hematology and Oncology products, has only approved one drug for the treatment of patients with, specifically for the treatment of patients with tuberous sclerosis complex, and that of course is everolimus for patients who have SEGA and for renal angiomyolipomas, and there's only one drug that I know of that has been approved for the treatment of patients with LAM which is sirolimus.

If you'll indulge me for a few minutes, I'd like to briefly talk about what we were thinking about as regulators when we were trying to determine whether or not to approve everolimus for the treatment of SEGA and renal angiomyolipomas, because I think they can give you a little bit of insight about how we approach trying to determine how, whether drugs should be approved or not and also to give additional clarity on sort of, what's been missing and what we're all now working toward.

So in 2010 we granted accelerated approval to everolimus for the treatment of patients with SEGA that requires a therapeutic intervention but could not be cured by surgery, and this approval was based on the findings of a very small, 28 patients, single-arm trial that showed about a third of the patients had a reduction in the at least by, at least 50% in the volume of their largest SEGA brain tumor. We also saw in this application that these responses were durable and that, over time, patients who responded-- weren't responding for just a week or two, they generally were responding for months or for longer. So taking all that into consideration, in addition to the safety profile of the drug, we felt comfortable granting accelerated approval to everolimus for that indication, and that was shortly followed by an additional approval for the treatment of renal angiomyolipomas, and then it approved approval of another form of everolimus called Afinitor Disperz, which is a suspension formulation for patients who couldn't swallow pills, and what these approvals had in common was that they were all based upon radiographic images showing us that tumors were shrinking and that they were shrinking to a point that we thought would result in tangible, clinically meaningful benefit to patients, and that these, the tumors that were shrinking were shrinking for long periods of time.

So at that point in time we felt comfortable with granting accelerated approval but recognizing that patients with TSC who had those types of tumors would likely be on the medication for a long period of time, we decided that we needed more information, longer-term data to better assess the duration of response that these patients were having, as well as the more chronic long-term potential safety issues that could arise when you're taking medications such as Afinitor for a long period of time. Ultimately, we reviewed the data back in 2016, we got long-term data from the company who produces Afinitor and after reviewing that data we got even better sense as to how durable these responses were for a good proportion of patients and we didn't identify any long-term safety signals that we thought could be problematic, either for adults or for children, who may be more vulnerable in some ways because of their developmental needs and trajectory, so what did we consider in addition to tumor shrinkage and safety profile that we got when we were thinking about the approval? We considered the potential for new or worsening hydrocephalus in patients who had SEGA if they didn't have other treatments. We thought about potential for complications due to alternative treatments, possibly such as renal embolization or need for nephrectomy in patients with renal angiomyolipoma. Morbidities that may be associated with renal angiomyolipoma themselves, such as hemorrhage or renal damage, and as you'll see if you look at our packages or we also noted in the renal angiomyolipoma indication, the clinical studies section, that talks about the benefits of treatment, we also included information about visible visual improvement in the skin manifestations of tuberous sclerosis complex in patients who receive everolimus, not for treatment of their skin but for treatment of the renal angiomyolipomas. As someone said, it was another side effect, but a good side effect, and so we talked a little bit about that in the product label, as well.

When we review data from applications to treat cancers or more benign tumors that can still cause medical problems such as SEGA and renal angiomyolipomas, we consider all the relevant information that's given to us, such as the adverse event information that's collected by physicians and investigators and clinical trials. We look at images radiographic images to see if we can determine whether there's a change in the way tumors are growing. When available, we'll also evaluate information relating how do treatments impact patient-reported outcomes such as pain, the incidence of complications of a disease, such as hospitalizations, changes in seizure frequency, and when needed at times and we're reviewing applications we do seek external input from people that we consider specialists in the disease, whether they be researchers who are working on that particular disease or from patients themselves who serve as patient representatives under a special government employee program.

So looking back at that approval for everolimus and looking at our product label for everolimus for patients who have SEGA and renal angiomyolipomas, what was relatively missing is information about how that the treatment impacted patients and caregivers themselves that's coming directly from the source rather than funneled through investigators and other study endpoints, and this is because, in the past, important information relating to patient experience has not always been systematically collected and presented, and the instruments that we've had available in our armamentarium have not been appropriately validated and qualified, such that we can really reliably interpret the information that we're learning from them. Dr. Woodcock touched a little bit this morning about one of the challenges to drug development is keeping patients on clinical trials, and so one thing that we've really been hampered by is a patient dropout because when, all of a sudden, we get a lot of missing data, then we don't know what to do with the information we have, and it's harder for us to draw conclusions, and as a result of this, the majority of labeling for drugs to treat cancers and other nonmalignant tumors such as SEGA and renal angiomyolipoma lack information about the patient experiences coming directly from the patient's themselves. In this case of everolimus, we were not able to include this information about how treatment affected patients' everyday lives, what toxicities they experienced, whether these toxicities changed over time, months on therapy, how bothersome they were, conversely, how treatment may or may not have helped them feel or function better, not just did it shrink their tumor or not, and that's frustrating for everybody involved, frustrating for us, I'm sure more than frustrating for you, and you're faced with these difficult treatment decisions.

So as Dr. Woodcock said this morning, we recognize the importance of systematically incorporating a patient voice throughout drug development, not just at the time when we're trying to determine whether to approve a drug. So from the very beginning, when we're talking about trial design, we really need in value to take the patient voice, the patient's perspective as part of that calculus that we're making when we're providing advice, and we now have a dedicated team in our office and in other offices of FDA that helps us provide more consistent, more timely advice to researchers regarding how best to collect and understand patient perspectives on the toxicities of treatments or on how treatments may benefit them with the goal of including this information in our product labeling to help patients, caregivers, and health care providers make treatment decisions. We also hope we'll hold public workshops at involved advocacy groups such as yours, researchers, patients, and other stakeholders to help discuss relevant topics related to drug development such as clinical trial endpoints for particular disease, and we're certainly open to doing that with you guys if you're ever interested.

So why is this meeting so important? From my perspective as a pediatric oncologist and drug regulator discussions such as the ones that took place this morning and will take place again later today are vital to helping us achieve our mission, which in essence is to get the right drugs to the right patients as quickly as we possibly can, and also helping to speed new innovations that will make medicines more effective, and safer, and, yes, more affordable, and also to help the public get accurate, science-based information to help them make the treatment decisions they need to make, and of course communication among all of us is needed to ensure that we're achieving these goals in the most efficient way possible and with the patient's interests foremost in our minds. There's no substitute for hearing directly from patients and caregivers how tuberous sclerosis complex and lymphangioleiomyomatosis-- I might have massacred that a little!-- how it impacts patient's health and your lives. What aspects of tuberous sclerosis complex and LAM would you most like to see treatments develop for, and to gain a better understanding of how these treatment decisions are made and what risks you're willing to accept for what potential benefits you can gain. That's really important for us because a lot of what we do is this risk-benefit balance, and to have your voice as part of that estimation and judgment is really very, very important, so gaining perspectives from patients and caregivers at meetings such as this one provides this critical information needed to strengthen our understanding of the burden that tuberous sclerosis complex and LAM and its treatments have on patients and families, the various ways that patients will try to manage their symptoms and side effects, and the range of considerations people take into account when making these difficult treatment decisions.

We're committed to carefully considering this input when advising sponsors on their drug development programs and when assessing products under review for marketing approval. The information we gain today will be used to help support our benefit- risk assessment for products under review in the future and may also be useful in the overall drug development process more broadly, for example, by helping us identify potential areas of unmet medical need for patients with TSC and LAM or by informing development and qualification of new patient-reported outcome measures that can be used in clinical trials of new treatments for those diseases.

When this meeting adjourns, we'll all come away with valuable information, but we're also committed to continuing engagement with you in the future in order to move things forward to recognize things don't stop here and they don't stop once the Voice of the Patient report is done. We're looking forward to many more productive interactions in the future. As Dr. Woodcock mentioned, we're still in the process of formalizing how interactions between FDA and patient groups should be undertaken, but in the meantime there's still multiple ways that we can work together and we're always open to suggestions, and feel free to contact us. So thank you again for your time, your openness, your candor, your courage, and your commitment to helping move the development of new treatments forward. We at FDA in return promise to listen and do our best to ensure that your voice and needs and opinions are reflected in our work. Thank you.

**Steve Roberds:** Thank you, Dr. Donoghue, for those insightful remarks and the compassion with which they were thoughtfully put together and delivered. We appreciate you and your colleagues being with us here today from FDA. It's now my pleasure to introduce our colleague from the LAM Foundation and a friend of mine to give you an overview of their research initiatives and to introduce our expert panelists who will provide the disease overview. Please welcome Sue Sherman.

**Sue Sherman:** Good afternoon. I am Sue Sherman, the Executive Director of The LAM Foundation, and I've been in this role for nearly four years now. I guess time flies when you have meaningful work. Let me begin by also thanking everyone in the room, our scientists, clinicians, drug developers, our FDA officials. I think we can all agree that we're buoyed when we hear leaders from the FDA like Dr. Donoghue speak with such enthusiasm about hearing from us and knowing that that will make a difference in their work, and most importantly thanking patients and families who've shared their stories, as this is the reason we're here today. I'd like to extend a special thank you to our partners at the Tuberous Sclerosis Alliance for extending the invitation to The LAM Foundation to collaborate and be a part of this groundbreaking meeting. Partnerships like ours are ones to be sustained.

So The LAM Foundation is a non-profit patient advocacy organization, and our mission is to urgently seek safe and effective treatments and ultimately a cure for LAM. Since 1995, The LAM Foundation has distributed $13 million directly to fund basic clinical and translational research projects focused specifically on LAM. That investment has, in turn, leveraged into an estimated 50 million additional dollars from other sources, such as the National Institutes of Health, the FDA, and the Department of Defense. So how does a small rare disease organization accomplish that? Simply, The LAM Foundation has partnered with patients and families to harness thousands of small donations and funnel that money into these research projects, while simultaneously working with patients to encourage them to become their own advocates, to become the research subjects of those funded projects, and to be leaders on their journey towards treatments, possibly a cure and a better quality of life along the way. Taken together, these two efforts and in less than 20 years this led to the 2015 approval by the FDA of Rapamune or sirolimus, the first effective treatments for LAM.

It is now my sincere pleasure to introduce Dr. Frank McCormack, who has been the voluntary Scientific Director of The LAM Foundation since its inception in 1995, and I would argue he has been the chief architect of the success of The LAM Foundation and its story. Dr. McCormack is the Taylor Professor and Director of Pulmonary Critical Care and Sleep Division at the University of Cincinnati College of Medicine, and having been given the honor of introducing my colleague and friend I will assure you he is an accomplished scientist with a long list of publications, awards, and has received many honors and accolades for his clinical work at the University of Cincinnati Medical Center.

By his own admission, Dr. McCormack believes that his work with LAM patients in LAM research and with The LAM Foundation have provided him with a rich professional and personal reward, so rather than take down his impressive CV, I thought I would share with you a quote from a person with LAM who's been treated by Dr. McCormack. "When you meet him, you are greeted with a warm and genuine smile that instantly assures you everything will be okay and you have hope for a future that is far from bleak. He sees you as an individual, not someone with a disease or another statistic. He will pull up a chair and listen to your story, let you share your concerns, and he will help calm your anxieties. He projects confidence, never arrogance, and believes that your care is his number one duty." LAM patients are incredibly loyal and trusting of Dr. McCormack because of his profound empathy, his sharp wit, extraordinary knowledge of the disease, keen curiosity, love of patient care, and his relentless dedication to defeating LAM. Please join me in welcoming Dr. Frank McCormack.

**Frank McCormack:** I wasn't expecting that, thank you, Sue, so much for that very kind introduction, and also to Steve and Kari for the invitation to speak here. It's a great pleasure to present this short synopsis of my experiences in the tuberous sclerosis clinic at the University of Cincinnati, and I have to let you know that I'm an adult pulmonary physician and I'm not really qualified to talk about the CNS and renal manifestations of tuberous sclerosis in any depth, but I've been an observer of what goes on in that clinic for some time now and I'll just share a few thoughts in that regard. It's been a real privilege to be part of this effort over the last 25 years or so that the pace of discovery in tuberous sclerosis and LAM rivals any in medicine. To have these FDA approvals and all of the scientific progress that they represent all occur over a very short period of time is truly remarkable, and I don't know of another disease, at least in pulmonary medicine, where this kind of progress has occurred.

With respect to the approval of sirolimus for LAM that Sue mentioned, here at last this was an investigator- initiated trial with no intent to get an indication from the FDA, and Pfizer was initially reluctant to consider taking it forward for approval, but with a lot of help from the FDA and with Pfizer's backing once the FDA showed interest, the approval followed very rapidly. The FDA encouraged us to apply for orphan drug designation, breakthrough designation. They helped us with planning the NDA submission as a non-commercial entity preparing something we've not done before, and then issued an approval within six months of submission, so the approval process was greatly facilitated by the FDA and we're very grateful for their help. By the way, the approval of sirolimus in LAM greatly facilitated approval in countries where the drug is not available unless it's approved by the government, so once it was approved, once the MILES trial occurred in Japan, took that data back and showed it to their own government it was approved in Japan rapidly. It was approved in Russia rapidly and in South Korea and it's under consideration in two or three other countries on the basis of FDA approval and that provides access to patients who otherwise wouldn't have had it.

This is a map of clinical manifestations of tuberous sclerosis through life and it's a little bit complicated but the manifestations that I see in the adult side in the tuberous sclerosis clinic include the neurocognitive issues and epilepsy, witness to them, I don't care for them, facial angiofibromas and other skin manifestations, renal angiomyolipomas, which can become quite problematic, and lung cysts, which occur in about 20% of patients by age 20 and about 80% of patients by age 40. However, symptomatic LAM only occurs in about five to ten percent of patients with tuberous sclerosis, so the fact that a person with tuberous sclerosis has cysts does not necessarily mean that that person is destined to develop symptomatic LAM.

LAM occurs in two settings. The one that everyone in this room is familiar with, the tuberous sclerosis complex- associated LAM, that represents only about 15% of the cases we see in adult pulmonary clinics throughout the United States. There are estimated 250,000 predicted cases worldwide, and in these patients the tuberous sclerosis mutations are found in the germline, and this disease is at least theoretically transmissible from mother to daughter, although that's a little nuanced, too, since it's kind of a two-hit event, but it is possible for a mother and a daughter both to have LAM. It's unusual but it can occur. That never happens in the other form of LAM, called sporadic LAM. This represents 85% of the cases that we see in clinic. It affects between may be as many as 10,000 cases worldwide. Tuberous sclerosis mutations are only found in the lesions, not in the germline, so we don't find them in peripheral blood except at very, very low levels that are hard, a little nuanced to explain, but we don't really find them with any regularity in circulating cells, and this is not transmissible from mother to daughter. So it's a little bit paradoxical that the less common form of LAM is the one we see most of in our clinics.

These are the manifestations of LAM, which include pneumothorax which occurs in about 70% of patients. You can see on this chest X-ray that this side of the chest is quite loosened compared to this side. That's because the lung is collapsed into this fist size ball right at the hilum. Lymphatic spread occurs, tends to spread through the retroperitoneal lymphatics. You can see these low-density lymphatic lesions surrounding the aorta. Renal angiomyolipoma occur in about 30% of the sporadic form of LAM in and about 60 to associated form, and chylothorax occurs in about 30% of patients with LAM, mostly in the sporadic form. It's very uncommon in tuberous sclerosis-associated LAM, and we're really not sure why there's that difference. On light microscopy, this is a normal photo micrograph up in the upper left-hand corner, you can see that LAM cells invade these alveolar septa and expand it, and they have this unusual spindle-shaped and sort of cuboidal morphology that stains with a very unique antibody called HMB-45 that's that was developed against melanoma cells, and nothing else in the lung stains with this marker except metastatic melanoma so it's very useful diagnostically. We don't really understand why this antibody staining occurs in LAM but it helps us with a diagnosis. Under low power, you can see this tremendous destruction of the lung compared to this photo micrograph up here with large cystic lesions surrounded by smooth muscle cells and also smooth muscle cell nodules remote from cysts. The average age of diagnosis for the sporadic form of LAM is about 35 years and the tuberous sclerosis-associated form is discovered earlier, because we know where to look. We know we can screen in this population and find it. It also occurs in some men with tuberous sclerosis, about clinic have cysts in their lung. It's very rare, though, for men to develop sporadic LAM, although it does occur.

LAM is a metastatic neoplasm. We'll talk a little bit more about that. The cell that populates the lung and destroys it arises from a distant source. We're not sure what that source is. The rate of decline in lung function in you and I is perhaps 1% a year after age 27. In a LAM patient the rate of decline is roughly 3 to 15% per year. In the tuberous sclerosis clinic, it seems to us that the rate of decline is somewhat slower. Dr. Moss has done a study to show that for patients matched for lung function, the rate of decline is about the same, but because we discover these patients earlier, perhaps we're under the impression that it moves slower. We're really not sure if they're exactly the same disease in terms of rate of decline. Once patients develop symptoms, it takes about 10 years for patients to become breathless. By 10 years, 20 percent are on oxygen and 10 percent of patients are deceased. The median survival varies between 8.5 to 29 years depending on whether you're looking at hospital- based cohorts or population-based cohorts such as those patients registered with The LAM Foundation.

We don't know where the source of the LAM cell is, but it appears to us that it arises in the pelvis or abdomen because the pattern of lymph node involvement follows a gradient from the pelvis toward the chest, so about 43-41% of patients with LAM have lymph node involvement in the pelvis and abdomen, whereas only about nine percent have involvement in the mediastinum and thorax. So it appears that some things arise in here, and we're very suspicious that the uterus may be a rich source of LAM cells, and there many case reports of LAM and the uterus. It would explain the gender restriction, but of course not the male involvement. So I see patients in two settings. I see sporadic LAM patients in my adult pulmonary clinic. These patients are 25 years and older and they really only have disease in the chest and abdomen and that disease includes LAM itself, angiomyolipoma, lymphangiomyoma, and chylous effusions. In the tuberous sclerosis clinic where I attended for the last always trying to get me to see younger kids, I don't feel very comfortable with that, the neurologic, renal, dermatologic manifestations predominated that clinic, of course, as we've heard all through the day, and compared to a sporadic LAM, tuberous sclerosis-associated LAM tends to be discovered early, tracked in this asymptomatic phase for some time. These patients we see year after year in clinic and there seems to be very little change from CT to CT. I don't know where the rest of that sentence was, but fell off somewhere. So in my adult pulmonary clinic, by contrast, where most of the patients are sporadic LAM patients, I may see up, actually, I think I need to back up for a second, no, that's right, I see patients who have lung cysts and the question is, is this LAM or is this some other cystic lung disease?

And we have a biomarker for that that's based on a vascular endothelial growth factor D which is overexpressed in LAM patients and very useful diagnostically. I often end up titrating the dose of sirolimus based on my assessment of lung function stability. That is, we track lung function over time, and as long as it's stable, we don't really try to titrate the sirolimus within any certain range. Sometimes very low doses are effective it with this drug, and then managing the side effects of the mTOR inhibitors, such as mouth ulcers, acne, lower extremity edema, elevated cholesterol, and we're learning more and more about these drugs as time goes on. Patients are corresponding on various web-based portals and we learned through them, for instance, that ovarian cysts can be problematic on this drug, and other things. So that's going to be a rich source of information going forward.

Sue was just talking to me about that at the break whereas in the tuberous sclerosis clinic I feel very privileged to have been part of this because it's a completely different perspective on this disease. We often again titrate the sirolimus or everolimus dose based on lung function stability. I find myself counseling young teenage women and their parents about screening for LAM and it's often a very difficult conversation because these families are often been through a lot already and now they have to deal with yet another tuberous sclerosis manifestation or at least the possibility of one that they may or may not have been aware of. It's difficult to break the news that the 25-year-old woman has a substantial burden of lung cysts. And we plan LAM management in this clinic. We try to determine if mTOR inhibitors are slowing LAM progression in cognitively impaired, nonverbal, institutionalized people in this clinic, as well, which is difficult, because these patients can't do CAT scans without anesthesia. They can't do pulmonary function tests, etc. Sirolimus provides durable stabilization of lung function.

This was the study that led to approval, and as you can see, the lung function in patients who took the drug was stable throughout the course of one year on therapy. Those who took the placebo lost about 11% of their lung function over that first year, and in the second year, lung function decline resumed in the sirolimus group and it paralleled the placebo group. So this drug works while you're taking it for LAM and when you stop taking it, disease progression resumes. And Dr. Moss just published a study, came out last month, that said that in his population of LAM patients, he had about 25 LAM patients that this stabilization of lung functions and patients who continuously took the drug was stable up for almost five years. They had, these patients have been losing about 190 cc's per year of their lung function, or about 10% or so of their lung, for more than 10% pre-rapamycin and that dropped by many-fold post-rapamycin to less than 25 CCs per year. Rapamycin is also effective for other manifestations of LAM, including these retroperitoneal lymphangiomyomas, which are surrounding the aorta here, they shrunk greatly on rapamycin treatment. So mTOR inhibitors have been game changers in LAM.

When I see a new patient with LAM, I tell her that she can be very optimistic that these drugs will stabilize her disease in a durable way, and on the low doses of sirolimus we're using in our clinic, side-effects are quite manageable, yet therapy is only suppressive. If this requires lifelong use, this is not a perfect solution, and some patients can't tolerate mTOR inhibitors and either fail to respond or cease to respond. So that's, in my experience, that's not a very common event, but it's a very troubling one since we only have one drug that's used in this disease. So I won't read these in detail, because it'll take too long, but basically we screen patients for LAM in the tuberous sclerosis clinic beginning at about 18 years of age with pulmonary function tests and high resolution CT, and we generally repeat the CT every five to ten years in asymptomatic individuals to see if there's any evidence of development of cysts. We also at every visit ask patients about exertional dystony and shortness of breath and counsel regarding smoking and estrogen use, and we treat patients who have moderate to severe lung disease or rapid progression with mTOR inhibitors. Tuberous sclerosis patients are candidates for lung transplantation, but in some patients, their comorbidities may impact their candidacy significantly, so in terms of next steps for LAM, we have an observational registry that's NIH- funded to examine the long-term safety and advocacy of sirolimus, and that's currently enrolling, the MILED trial is a repeat of the MILES trial you saw earlier in patients who have normal lung function and who are asymptomatic, so we're using early low- dose sirolimus to try to prevent the development of LAM in a prophylactic way, and that's going to start enrolling this month. There are many other trials that are either launching or underway, including an inhaled rapamycin trial, which is particularly attractive for limiting systemic toxicities. We have a network through The LAM Foundation of fifty-five clinics around the world that are tracking over 3,000 LAM patients, and we've used this network to enroll for trials, to collect samples, and to share clinician expertise and patient vignettes to learn more about the disease together. The tuberous sclerosis clinics overlap significantly with the locations of LAM clinics at academic health centers around the United States and we're working to try to better integrate these entities and in some cities, where the clinics may even be on different sides of town, one of the objectives that this meeting is to try to develop plans for multidisciplinary approaches by combining forces in clinics where there are both LAM and tuberous sclerosis clinics in the same city.

So with respect to FDA priorities, we're looking to the FDA for help with development of remission- inducing therapies, as they helped us with sirolimus, better diagnostic, prognostic, predictive, and surrogate biomarkers. We have a very good diagnostic biomarker and we need more, and there's a talc shortage that's compromising our ability to do effective pleurodesis, that I'm not sure if the FDA is aware of, but it's it's significantly impacted our ability to take care of LAM patients, just in the last few months. So some of the disabilities that are seen in tuberous sclerosis clinic, including the cognitive, behavioral, and mental impairments are not well represented by a picture. These issues dominate the adult clinic that I am a guest in, and I would have to say, as I mentioned this morning, that a significant number of families say that their cognitive-behavioral issues have improved somewhat, or measure[ably] or noticeably on mTOR inhibitors, but of course these are sometimes small changes, and although seizures are problematic in adults, or less problematic in adults than children, they remain a significant cause of morbidity in adults, and according to my colleagues David Franz and Darcy Kruger, sometimes community neurologists can become inured to long-standing seizure pattern in adults and accept things as they are, so there's more work that needs to be done to take aggressive approaches to seizures in adults in clinics that are not focused on tuberous sclerosis. And most brain tumors durably shrink on mTOR inhibitors, as Dr. Donoghue mentioned, and brain tumor resections have now become rare at our institution, which is quite remarkable.

So in terms of TSC guidelines, of course, for all subcategories, offering genetic testing and family counseling is important. TSC guidelines recommend obtaining brain MRI every one to three years in asymptomatic tuberous sclerosis patients younger than or TSC-associated neuropsychiatric disorders, continues into adulthood, and that's an important point to emphasize. Renal angiomyolipomas are mesenchymal tumors that are composed of abnormal blood vessels, immature smooth muscle cells, and adipose tissue. And they appear in childhood and tend to become more problematic with time. They're present in only a minority of sporadic LAM patients, but in most patients with tuberous sclerosis, and they become large bilateral, and problematic in patients with TSC-LAM. Renal cancer can develop in a subset of patients. Renal failure due to cystic and infiltrative angiomyolipomas occurs in a fraction of patients. It's important to control hypertension and avoid renal toxic meds, of course. Treatment results in AML shrinkage in two-thirds of patients, and stabilization in most others, and it remains to be proven that mTOR [inhibitor] treatment significantly decreases the risk of hemorrhage. I believe. I might be corrected about that if there's a nephrologist in the audience, but that's my take on the literature. Up to 35% of the patients with tuberous sclerosis have at least some simple renal cysts, and 5% have polycystic kidney disease, that's due to a deletion in the gene that's next door to tuberous sclerosis gene 2, and treatment is generally supportive, including control of hypertension.

So in terms of renal tuberous sclerosis guidelines, it's recommended that patients get an MRI of the abdomen every one to three years for the lifetime of the patient to assess growth, because these tumors do tend to slowly grow. Blood pressure and renal function; blood pressure needs to be carefully modulated. Embolization followed by corticosteroids is first-line therapy for angiomyolipoma presenting with acute hemorrhage, and nephrectomy happens way too often in the community and needs to be avoided. There are other, better ways to approach problems with TSC-related renal disease. In patients who are asymptomatic, we generally treat those whose AML is growing and 3 centimeters or larger in diameter. And selective embolization or kidney-sparing resections are recommended for those who have continuing problems.

So quickly, dermatologic manifestations of TSC affect almost all patients, and if you ask younger patients, this is the highest priority for many of the teens and young adults, and I guess that's not a surprise, when you think about it, but it does wake you up when you think, sometimes you have to ask the patient what bothers them most, instead of assuming you know what bothers the most. These have historically been treated by a blade of methods, including laser and camouflage make-up. Recurrences are common and it's difficult to execute in cognitively- and behaviorally-challenged patients. These are some of the manifestations, including subungual fibromas, which are very common and get worse in adulthood. Skin manifestations tended to improve in patients in the EXIST-1 and EXIST-2 trials, and patients who are taking the oral everolimus therapy, and case reports have suggested that systemic and topical sirolimus works to reverse these tumors of the face, and in fact, a randomized trial of topical sirolimus is soon to report, and I think many of us are anxiously awaiting that paper. So in patients with skin and dental manifestations, a full skin exam is recommended. Dental exams are also recommended because these patients develop the gingival fibromas and also dental pitting. Annual skin exams and dental exams are important, and rapidly changing, disfiguring, or symptomatic tuberous sclerosis-associated lesions should be treated as appropriate for the lesion and clinical context, with approaches that include surgical excision and possibly topical mTOR inhibitors, pending the results of this trial. So I'd just like to acknowledge everybody who works on tuberous sclerosis at the University of Cincinnati and Cincinnati Children's Medical Center. I thank you again for listening.

**Steve Roberds:** Thank you, Dr. McCormack. We appreciate this overview, and it will be really helpful to facilitate the rest of the discussion for this afternoon. You've certainly led the field in the development of clinical treatments and care for LAM, and we are very grateful to have you be a part of this meeting. So now that we have an understanding of the purpose of today and of TSC and/or LAM manifestations, we're here to get to the patient-driven part of our program, so I'd like to welcome back James Valentine, a close friend of the TS Alliance, who has helped in the preparation and planning for today's meeting. James, for those of you who were not here this morning, is an Associate at Hyman, Phelps and McNamara in Washington, DC, where he assists the industry and the patient groups in terms of regulatory issues and interactions with the FDA, including new drug and biologic development and approval issues. He previously worked at FDA's Office of Health and Constituent Affairs, that was previously known as the Office of Special Health Issues, where he facilitated patient input in benefit-risk decision-making and served as a liaison to stakeholders on a wide range of regulatory policy issues, including helping launch the Patient-Focused Drug Development program. James.

**James Valentine:** So good afternoon, everyone. It's great to be back up here. Hopefully those of you who were here in the morning are well fed and caffeinated, and I welcome those of you that just joined us. So as has been previously mentioned, this morning we focused on the patient's experiences and preferences for infants and children affected by TSC, and this afternoon we're going to be exploring those patients' experiences and preferences related to those of you that are adults with TSC and LAM. We are following a similar format that we did in the morning, but since I expect a number of you have joined us, we're going to start kick off by walking through what how our discussion is going to go and how we're going to seek input from all of you this afternoon.

So this meeting, this afternoon session is divided up into two topics. Our first topic is going to focus on the symptoms that matter most to you. So we're going to be exploring topics that relate to what are the most significant impacts of TSC and LAM on your day-to-day life, how the symptoms of TSC and LAM affect your ability to do specific activities in your everyday life. We'd like to hear from you about how your symptoms affect you on your best days as well as your worst days, and how these symptoms, manifestations might have changed over time. We'll then transition into our second topic, which builds on that, which looks at current and future approaches to treatment. So we're going to be asking you what you use, whether that be drug or some kind of other medical treatment, or even things outside of medical treatment like lifestyle modifications or diet and exercise that help you treat or manage your TSC or LAM. We want to know how well those treatments work to help treat the burdens that you talked about in topic 1. We also want to know what are some of the biggest downsides to those treatments, and ultimately we're going to ask you to weigh in on what you would like to see from future treatments. Basically, short of a cure, what is it that you ideally would look for in a treatment? The way that we're going to do this is, we have a series of ways that we're going to solicit your input over the course of the next couple of hours.

We're going to start out each of our topics with a panel discussion. So this is going to be a panel made up of your peers, patients and caregivers with TSC and LAM, and the idea here is to set a foundation for the rest of our discussion that will involve the rest of you in the room. And just so you're aware, the panel is selected to reflect a range of experiences with TSC and LAM in adults to kind of serve as a jumpstart to the range of issues that you all also might experience, but also allow us to build on with your experiences that might be different from what is heard on the panel. We'll then transition for each of our topics into a series of polling questions.

You should have had a clicker on your seat when you came in. If you didn't, you can raise your hand and someone will bring you one to use through the course of the afternoon, and I see at least one hand raised, and so these are questions that will allow everyone in the audience that is a patient or a caregiver to provide some input on the larger questions that we have for you. Again, this is to aid in our facilitated discussion that we have, and this is actually something that in addition to those of you in the room, those of you that are participating on the web are also able to do, and we'll go through the instructions for how you'll be able to participate once we get to our first set of questions. We do ask that only patients or caregivers of patients use this polling question, so if you came in here from FDA or industry or you're a clinician and you sat down on a clicker, just ignore it and no need to respond to the questions. After that, we'll then open it up to the broad audience discussion.

The TS Alliance and LAM Foundation have put together a series of questions that reflect what it is that is, as we heard earlier, is important for FDA to hear to help inform their decision-making. We're going to build on the questions that we've discussed with the panels and through the polling questions and for that session we'll just ask that you just raise your hand. I'll be facilitating that discussion, so I'll call on you. We just ask that you state your name before you provide your response, so that way for our purposes of tracking your responses throughout the meeting, we can kind of combine any responses that you might have shared over time as we put together the Voice of the Patient report, which is the official meeting summary that will be supplied to FDA.

Finally, for those of you that are on the web, unfortunately we won't be able to have you participate in the audience discussion in the live format, but you are able to provide your comments through a number of social media channels, so if you're online you can use the hashtag #PFDD on Twitter. If you're on the YouTube livestream page, you can provide comments there, or you can go to the TS Alliance Facebook page, where there's a comment that you can respond to that relates to this meeting. Although we may not be able to read or summarize all of your comments on social media, we want you to know that those they will be incorporated into the summary report, and if you do happen to comment, we will at times incorporate your comments live as we move through the meeting.

One last piece of business before we move into our first set of polling questions is, we do have some ground rules for our participation today. So we do encourage all individuals and caregivers affected with TSC and LAM to participate. In fact that's who we're hoping all of you will participate that are here. We have a number of other stakeholders that were invited to participate in listening mode. That includes the FDA, industry, academic researchers, and clinicians, so there if you're one of those stakeholder groups, we ask that you respect the voice of the patient and caregiver and allow this dialogue to be used, the time that we have today to be used for their input.

The discussion is going to focus on health effects and treatments for TSC and LAM. There's going to be a number of other topics that might fall outside of the scope of that, for example, access or payment issues to various treatments. We've formulated the questions to try to hone in on what is most important to FDA, so just please try to keep your comments focused on the questions that are being presented to you. We do recognize that the questions that we're asking are very personal, and at times can be emotional, and so we just ask that you please be respectful of one another as you provide your comments and please wait to be a called on by me to provide your comments so we can make sure to try to get through as many of you as possible. And then, just so you know, if you're not able to provide all of the input that you wanted today, maybe we just didn't have time, maybe as you're walking home or traveling home you think of something else that you wanted to provide, or if you're watching the recording of this meeting and you weren't even able to participate, there will be a SurveyMonkey link, it's in the program, that you can use to answer the topic questions for today, and responses to that will also be included in the summary report.

So with all of that we will now move to our first set of demographic polling questions. I will first walk us through the instructions for how to do this, and then we'll have you answer the questions. So we'll start here. We'll start with our online users. One thing you may notice if you're online is that there is about a 30- second delay in the audio/visual, and so if you're using the online polling software, you'll notice that the polling questions may appear earlier than they do in the audio. Feel free to please answer the questions as soon as they pop up, since we're only going to have them up for your response for a limited amount of time. For those of you that want to use, are on a computer and want to use your internet browser, again, patients and caregivers only, you can go to www.rwpoll.com and enter tsa621 to join the session. Alternatively, you can use a smartphone app. So you can download the ResponseWare app, both on iPhone and Android, and if you open once you download and open the app again, enter tsa621 and that will join you in the session. For those of you that are in the room, it's a little simpler. You'd have a clicker at your seat. When we progress through the questions here in the room, just use that to respond. You'll just click the button that corresponds with the same number on the screen. Some of the questions will be a single response. Some will be selecting more than one. As long as you hit all the buttons well before the timer runs out, all of your responses will be collected. Once we finish that, the results will be displayed and we'll actually discuss them in it. That'll allow us to build on it in our discussion.

So our first question, simple one, where do you live? So the responses are, enter one if you're from the Washington, DC metro area, including the Maryland and Virginia suburbs; two, if you're in the United States but outside of the DC metro area; or three, if you're outside of the United States. Alright, so it looks like about 70% are from the United States but outside of the DC metro area, so that's great participation for a meeting here in DC to have you join us. Looks like about a little less than a quarter of you are from outside of the United States and then ten percent of you are locals.

Our second question is one where you can respond to all that apply. To help us identify who you are, the first response is you have been diagnosed with TSC; two is if you've been diagnosed with LAM; three if you're a caregiver of someone who has TSC; or four if you're a caregiver of someone who has LAM. Okay, it looks like the most of you that are here are caregivers of those who have TSC. It looks like we also have good representation of our other subgroups within the population here, so we have individuals that've been diagnosed with LAM as well as those that've been diagnosed with TSC or take care of someone with LAM.

So now we're going to move into our first topic, so I invite our first panel for the afternoon up to the stage. You can come right on up. So here we're going to dive into topic one, which I mentioned is living with TSC or LAM. This is going to be a dialogue about the burdens and symptoms of the diseases that most impact your daily life, and also the impacts on your various activities in daily life. We have a great panel lined up for you today. We have Mary, Seth, Arlene, and David, and I'll go ahead and turn it the mic over to Mary to kick off the panel.

**Mary Stojic:** Good afternoon. My name is Mary Stojic and I have sporadic lymphangioleiomyomatosis. My symptoms include chronic bronchitis, shortness of breath, and small AMLs on my kidneys, but my most dramatic symptom has been repeated lung collapses. The pain when it collapses is quite sharp with each breath and the pressure in the chest means no restful sleep. I have had four surgeries to pleurodese (glue) my lungs to the chest wall to keep my lungs from collapsing, and many smaller, what I call "nuisance pneumos" which means they don't require medical intervention. Whether the collapse is large or small it requires four to six weeks of rest, no physical activity, and lots of creative ways to accomplish family activities while not being physically active. Then it takes weeks to rebuild to normal energy levels. A diagnosis of LAM means constant worry that a chest twinge could be the sign of another collapsed lung, with more chest tubes, surgeries and rest I have had to change, postpone, and cancel family vacations because of ill-timed collapses that required medical assistance and time to heal.

As the years have progressed, I have become more and more noticeably short of breath when exercising and performing regular routine activities around the house. I stack items at the bottom of the stairs to reduce the number of trips upstairs to conserve energy. Walking and talking simultaneously is an aerobic activity which causes visible shortness of breath. If it is humid, I stay indoors or walk very slowly. These issues were a problem when my daughters were young. As I looked healthy, many people didn't understand my request for favors, such as rides for my daughters when I was recovering from bronchitis or collapsed lungs, permission to park closer to events so that my energy level wasn't all used walking to and from the event, especially on humid days. It was hard to sit and watch other parents keeping the children, instead of participating myself.

An example of why I had to sit or move slowly during the humid days was I was helping my daughters load their horses onto the trailer at the end of the state fair. The weather was horribly hot and humid, and the truck and trailer were parked on an incline. We were being urged to load the horses and all the equipment quickly to keep the line moving. With a combination of heat, humidity, and walking quickly uphill, I ended up doubled over, gasping for breath. The volunteers helping to keep the horse traffic moving came over and asked, "Are you all right? Do you need medical attention?" Of course, I couldn't use the teachable moment, because I couldn't breathe to explain about LAM. That was about eight years ago, and most days I'm able to move slowly enough to not have such difficulties with my shortness of breath, but it has gotten worse. Even so, many friends and family members do not notice, as I simply slow down to compensate.

I do not want to limit my activities further. I want to continue my life. Since my early 20s, cold viruses usually progressed into bronchitis several times each year. I've had to learn not to wait too long before seeing the doctor for an antibiotic. Earlier treatment can mean the difference between one round basic antibiotics, or a second or third round of stronger antibiotics, more time down from work and family activities. Fatigue has been another reality in my life with LAM as well as for many other LAM patients. It saps our energy, which can impact our families, career choices, and thus, for some, financial status. As a college graduate, I did not work outside the home other than the occasional mornings at the local nursery school to conserve energy to be able to participate in my children's lives. I've had to learn to manage my activities. Routine activities like grocery shopping have become events to be planned. It requires a lot of energy, the shopping, the loading, the unloading, the car sorting, storing, and then preparing the meals.

With my daughters grown, I decided to return to work, although my former career path, cross-cultural training, was not an option, as it would be too physically demanding, standing, talking, and leading training sessions. I found a job that is sedentary. This way, I can reserve some energy for my husband in our life together with limited exposure to germs. No retail job or working with children. My goal is to find a job that I would be able to do even if my lung function drops. I continue to manage my work and personal schedules daily, weekly, and monthly, so as not to have too many activities, which would exhaust me and lead to bronchitis or another collapsed lung.

As difficult as the diagnosis of LAM was, I was blessed that I had not been diagnosed in 1985 at the age of 21 with the first collapsed lung, but rather at age 34, after I'd given birth to our three daughters. I was spared the difficult decision of whether to risk pregnancy with the diagnosis of LAM. Many of our LAM patients are diagnosed while pregnant or early in marriages as they are starting families. I only had a small collapsed lung during my second pregnancy, before my diagnosis. I hope that with the mystery of LAM progression, we can find a cure or at least find answers why some of us progress quickly while others are more chronic, so that we can make educated decisions about pregnancy. Lately I've noticed I am more short of breath when walking. Bending over to garden has become difficult, as I can't breathe easily. Over the years I have reduced the amount of plants and flowers in my garden. This year I may not plant a vegetable garden. I may need to make some difficult decisions: fewer hours at work, fewer activities as a volunteer, to stay healthy and yet live my life. Thank you for listening.

**Seth Fritts:** Good afternoon. Thank you for the opportunity to speak today. My name is Seth Fritts, I'm 48 years old, and I come from Denver, Colorado. I'm honored and humbled to have the opportunity to present my story to you in hopes that it helps to significantly improve the lives of those of us affected with tuberous sclerosis complex. My journey with the disorder began when I was 8 years old and my mother brought me to the dermatologist to inquire about the strange acne on my nose and cheeks. I remember sitting in the waiting room looking at posters of people with acne and wondering why my skin didn't resemble those that were in the pictures. A few minutes later, I was called into the exam room and met with the physician. After my mother explained why we were there, the doctor took a quick look at me and within seconds made the declaration, “You have tuberous sclerosis complex.” He then asked my mother if I'd ever suffered from seizures. My mother replied that I had not, to which his response was, “You're lucky he's not profoundly retarded and suffering from frequent seizures.” A few minutes later, the doctor invited all of his colleagues into the room and began shooting Polaroids of my nose and face, while his colleagues used a Wood's lamp to search for shagreen patches on my back and legs. Over the next two years, I endured test after test to look for tubers on my brain, heart, kidneys and lungs, while regularly visiting with my dermatologist to try the newest torture therapy to remove the angiofibromas on my nose and cheeks.

After a few years of intense screening, no additional symptoms were found, and I went on with a relatively normal life. From this point on, my mother and father, who worked in the insurance industry, did everything they could to avoid a formal diagnosis of TSC, as they were worried I would eventually be excluded from coverage because of my pre-existing condition. In my mid-twenties and again in my early thirties, I developed ungual fibromas under my big toes that were removed surgically with minimal discomfort and a relatively short recovery period.

In my late thirties, I was in excellent physical condition; I had met and proposed to the woman I would marry; and just accepted a position to launch a new drug for another rare disease. I was taking a martial arts class and just finished for the night. After leaving the gym, I noticed a strange dripping sensation in my lower back. I didn't feel any pain or discomfort so brushed it off as inconsequential. A couple of weeks later, I went in for my annual physical where I provided the usual urine specimen. A few days later, I received a call from my doctor telling me he wanted me to go in for some additional testing as they found some red blood cells in my urine. After a variety of imaging studies, it was determined that I had 3 angiomyolipomas on my left kidney. An angiomyolipoma, also known as an AML, is a highly vascularized fatty tumor that is common in patients with TSC and can become life-threatening if it breaks open as it did in my case. I realized then that I should probably inform my providers of my early childhood diagnosis.

I was then referred to a urologist who reviewed my case and scheduled me for a partial nephrectomy. Since I had been working in healthcare most of my career, I knew I should get a second opinion and spoke with a good friend who is a surgeon. He informed me the standard of care for an AML was embolization, not surgery. I then spoke with my urologist who talked me out of embolization because he didn't feel it was effective in treating AMLs. I chose to move forward with the surgery and spent the next several weeks recovering in excruciating pain. It was difficult to sleep, and generally challenging to do anything including work. To this day, I wake up almost every night in intense pain from the scarring I developed from that surgery. My doctor also advised me to quit contact sports such as hockey and martial arts to avoid rupturing future AMLs, which has had a significant impact on my health and overall quality of life.

A year after my recovery, my wife and I decided we wanted to have a baby and began looking into genetic counseling. I met with the geneticists in New York where I provided a sample of my blood and sent it off for very expensive testing. At the same time, I was referred to a neurologist, where I underwent an MRI of my head to check for brain tumors and was sent home with a portable EEG to assess for seizure activity. A few weeks later, we came back for a follow-up appointment and were told that the genetic test was inconclusive, but the MRI showed I had four tumors on my brain. Fortunately there was no seizure activity found with the EEG. My wife and I decided to utilize a sperm donor to avoid the chances of passing along this complicated disorder, and in 2011 we were blessed with the birth of our beautiful daughter. After moving back to Colorado in 2012, I met with a new provider to reassess my kidneys. At this time, the AMLs on my right side had grown enough to be eligible for removal. This time, I opted for embolization. The procedure was quick, with minimal discomfort and a relatively fast recovery period. As you've heard from my fellow panelists today, the diverse clinical manifestations of this disorder are profound. I consider myself lucky, but as with all of us with TSC, I constantly wonder what's next. Thank you.

**Arlene Bandstra Achterhof:** Good afternoon, I’m Arlene, mother to my 53-year-old daughter Ellyn. Our family lives with a complex disorder. Ellyn had her first seizure when she was four months old. I'll never forget the warm sunny spring afternoon when she awoke from a nap and in my arms her head and arms made a sudden jerking movement. These sudden movements continued whenever she woke from her naps. I was a young mother, only two years after having graduated from nursing school, but I didn't know what this was. After I called to the pediatrician, it was arranged for our baby to have an EEG, which showed that our sweet baby girl had a seizure disorder and she began to take anti-seizure medication.

We began a life-changing long journey. Ellyn's development was slow. At 18 months she wasn't walking. It was decided the medication was causing sedation. The dose was decreased and within a few days she began walking, but gradually it became clear that she was developmentally delayed. By then our family had grown to include a brother and a sister. We blended a life of preschool, family activities, frequent seizures, doctor visits, and seizure medications. At the age of about 12, a new neurologist ordered a CT scan that revealed the abnormal characteristics of a rare disorder, tuberous sclerosis complex. Signs of this disorder were apparent at birth, but were not recognized by our doctors up to this time. The doctor told us that she would probably not live beyond her 20s.

Managing Ellyn was not easy. She was very active and impulsive, but she wanted to do what other kids were doing. Once she climbed the ladder to a tree house in our backyard. I went looking for her, found her walking to the house crying with her arm hanging by her side. She had fallen and broken her arm. There were other times when she got out of the house unnoticed that led to serious situations. Living with Ellyn was difficult for her younger siblings. Ellyn played the same music over and over again. She had trouble sleeping, which created problems for her sister with whom she shared a bedroom. When Ellyn was that I needed help with her care because I was working full-time and couldn't take care of her by myself. At that point Ellyn moved to a group home, but she has always come home for the weekend. Yet she cannot be left alone because of her seizures and her need for assistance with daily activities.

In the last year her seizures have worsened. Ellyn began to have generalized tonic-clonic seizures for the first time. About two months ago she had a tonic-clonic seizure in the bathtub. I was in the bathroom with her, I heard her yell, and she leaned her head back. Her arms and legs were jerking. Then she became limp and she was not responding. I was about to call 911 when she began to recover from the seizure. She was later admitted to the hospital for several days of continuous video EEG monitoring. The EEG showed increased seizure activity compared to the previous EEG’s. Ellyn had a VNS and those settings were increased with a plan to add another anticonvulsant if there was no improvement, but in the past few weeks Ellyn has had two falls due to seizures. She hit her head on a table at her work services program, causing a black eye, and a week later, she fell, hitting a kitchen table in her group home, causing a fractured clavicle. A third anticonvulsant was added to her meds, but this med has caused serious unsteadiness and mood changes.

Several years ago we purchased a hockey helmet to protect her head during falls, yet in these recent falls, she's not protected from injuries and broken bones. She is becoming more and more fearful of walking alone. She reaches for a hand when she's walking, wanting to know that someone is nearby. She seems to be more fearful in general. When we leave a room, she will get up to find us. We are concerned and frightened about her future. We tried all the anticonvulsants and treatments. We need something new. Reviewing our life to tell our story has brought sadness and tears to our entire family.

**David Stegemann:** Hi, my name is David Stegemann and I'm 19 years old. I was diagnosed with tuberous sclerosis at the age of nine by a dermatologist. He saw my facial, my facial [angiofibromas] and a white patch of skin on my abdomen and started asking if I've ever had seizures. I'm affected by tuberous sclerosis in my brain and kidneys. I consider myself to be a very lucky person because while living with TSC, I've not experienced any experience as much as the debilitating symptoms that so many kids would TSC have to deal with. Because I've been so lucky with TSC, with my symptoms, I've never taken any drugs to help with my disease.

I played I played three varsity sports in high school. Basketball, football, and lacrosse. I'm currently playing football in college as a tight end at SUNY Cortland, where I'm majoring in Exercise Science. Playing sports has always been a passion of mine. When I was diagnosed with TSC, my parents and I had to go make a big decision about how to handle playing contact sports or even playing them at all and how to handle my TSC. My parents told me something that I'll never forget: you might as well do the things you love and wait to see if something happens, instead of not doing that you love because you're afraid of something happening. Sports have taught me how to lead, how to work hard, how to be a good teammate, and how to put a for my team. There's also allowed me to meet some amazing people and some of my closest friends.

I have annual MRIs done on my kidneys and brain to determine if my TSC tumors have grown or changed. As for my brain I have a bunch of cortical tumors and subependymal nodules. I've been hugely lucky that these tumors haven't changed since I was born and that so far I've never had a seizure. My kidneys the scans have always shown some new tiny lesions, but nothing it but nothing that requires treatment.

However, the summer going into my senior year of high school, I received the results of my kidney MRI and it wasn't good news. The doctor said that I had renal cell carcinoma on my right kidney and the mass was six and a half centimeters. Being a seventeen-year-old and hearing the word cancer being applied to you, wiped all emotion off my face. They told me the best treatment for the cancer was to basically cut off the tumor and basically about half my kidney. On the day of the surgery I was taken to pre-op and my surgeon came in and said change of plans. He wanted to do a biopsy instead of removing half my kidney. He sent my scans to a whole panel of doctors to review because he wanted to make sure what it is. One of the experts told him that my tumor could be a type of rare TSC tumor that looks just like cancer, because it doesn't have any fat in it. I had a biopsy done and it confirmed that my tumor wasn’t renal cell carcinoma, but a rare form of tumor called fat poor angiomyolipoma and the treatment for that would be to embolize the tumor. Apparently this is a big issue with radiologists because they don't know about these type of TSC tumors and misdiagnose them as cancer, which causes a lot of potentially unnecessary kidney surgeries. The doctor then told me when they went to embolize my kidney tumor, there was a there was a really big aneurysm in the blood vessel that fed the tumor and the embolization hat was pretty challenging. Another crazy thing is that these tumors can create their own blood supply.

Given all that, I was again very lucky because overall the surgery was a success. I recovered from surgery and went on to play my senior football and achieved second team all-state, first team all-League, and also central New York as a tight end. I then played my senior in basketball and lacrosse and was a captain for all three teams. I went on to win my second sectional championship in lacrosse making me the only athlete in the history of my high school that went to sectional lacrosse championships. I'm here to tell you about my life with TSC and also how to tell you how scary the future is for people like me. I'm pursuing my dream to play college football, but I know that my TSC makes it even more dangerous for me than for the average athlete. I'm worried that my kidney tumors will continue to multiply and grow and then I'll have a ton of invasive and ongoing medical treatment and surgeries as I get older. I'm worried about how I will have to pay for my medical care by at the age of 27. TSC is a pre-existing condition. What if I can't get insurance or can't afford it? I worry about having children and hope that genetic research of TSC continues to be advanced and supported. I'm happy and share my experience I'm happy to share my experiences with you and hope that my perspective of TSC helps you better understand the disease and its impact on people and on the people who live with it. Thank you.

**James Valentine:** Thank you to all of our panelists for being the first to share this afternoon, and their very personal and difficult short stories to share. I know it's been difficult putting words to paper in preparation for today, so thank you. We're now going to turn to our first set of polling questions for topic one, so you can pull out your clickers if you're in the room. So we'd like you to respond to the first question which is which three TSC and LAM conditions or symptoms have had the greatest impact on your life as an affected individual or as a caregiver? The options are 1. epilepsy, 2. lung issues, 3. kidney issues, 4. skin issues, 5. developmental delay or learning and memory issues, 6. behavioral communication and social problems, 7. anxiety or depression, 8. tumors such as SEGAs, 9. heart issues, or 10. some other issue that's not listed above. Okay so it looks like, those top three conditions or symptoms related to TSC or LAM that have had the greatest impact, the most frequently rated one is epilepsy, closely followed by 6, which is behavioral, communication or social problems, as well as developmental delay or learning and memory issues. Kind of the next tier, includes kidney issues, skin issues, as well as anxiety or depression. We also have a number of you that rated, 4 was for skin issues, sorry, and then also a number of you rated brain tumors. Nobody rated heart issues as a top three impact and a few of you noted other. And if you were one of those individuals I hope you'll raise your hand to share what those were when we get to the audience discussion.

Our second question for you is about which of those same series of outcomes, if you could have meaningful improvement in one of those, would have the greatest impact on your life as an affected individual or caregiver? Alright, when asked to select one TSC or LAM condition or symptom that if there was a would have the greatest impact if there was an improvement, the highest rated single symptom or issue is lung issues, followed closely by 6 which is behavioral, communication, or social problems, not too low rated as 3 & 4, are the epilepsy and kidney issues, and then it looks like, we have some people that selected each of the other options except for skin issues and heart issues.

So with all of that in mind and what we heard from our panel, we'd like to hear from you in the audience about the health effects and daily impacts of living with TSC and LAM. I’ll read through the questions that we're going to be discussing, and then we'll turn it to you the raise your hand and provide some of your experiences for us.

So, our first question is, if all the symptoms that you or the person you care for experiences because of TSC or LAM, which one of the three symptoms have the most significant impact on you or the person you care for’s life? Building on that, are there specific activities that are important to you or the affected person you care for that you cannot do at all or as fully because of those symptoms? And kind of related to that is, how do those symptoms and negative impacts affect your daily life on the best of days and how is that compared to the worst of days, and also how have these symptoms changed over time, and then finally what worries you and the or the person you care for the most about that person's condition? So with that I'll come down off the stage here and start to explore. If you could share with us what you either selected in the polling or maybe if it was something else that wasn't listed on the list. What aspect of living with TSC or LAM has had the greatest impact on your life? It could certainly be something that has been shared by our panel, but whatever you pick, please let us know why. And I saw hand in the back, again remember to please state your name and also let us know if you're affected by TSC and/or LAM.

**Eleni Evangelidi:** Hello, my name is Eleni. I'm affected by TSC, LAM and the polycystic renal disease, so one of the symptoms of course which is more important with me is with a kidney at the transplant, so of course it is the most important, but others that are also really important, the anxiety and depression. I would say and the memory defects and yeah what's more worrying what worries me the most is what will come in the future because for the moment the LAMs doesn't bring any misfunctioning but we don't know how it will be in the future. Are there particular things about your progression of disease that worry you? For the moment I do take everolimus but just for the transplant, so it's not exactly the same dose. I suppose like for the LAM. But we have to check at the end of the year if there is any change of the lungs. So for the moment, I'll continue the everolimus, but of course I would like to have a kid next year and I will have to stop everolimus and see what comes. Sure sure. Thank you. For me two symptoms that weren't on that list were lymphatic issues and sleep. So those are my two biggest challenges of the course of LAM.

**Nicole Wipp:** I'm Nicole Wipp, by the way, and I have LAM and so those have had the most significant impact on my disease and my treatment of my disease and how it affects me.

**James Valentine:** Can you describe how the lymphatic issues have manifested and how that impacts your daily life?

**Nicole Wipp:** Well I think the problem with the lymphatic issues is that it's how it impacts your daily life is somewhat elusive because we don't really have any markers related to what that means. For me, initially, I had chylothorax, so and it was very pervasive, but I do believe just based on things, I have no other, zero other health issues besides LAM, and so anything that I experience is to me is attributable to LAM, whether or not that's agreed by the medical community or not. And the sleep is a big problem, is probably my very first major symptom and it continues.

**James Valentine:** And do you know what causes issues with sleep?

**Nicole Wipp:** Nope, sleep studies, nothing has been given me, so but I know just anecdotally from other LAM patients that sleep is a massive challenge for many of us and then of course other behavioral problems that I have as a result of a lack of sleep, but it’s a problem I think for anybody with a chronic illness.

**James Valentine:** And has it been consistent over time, having problems with sleep, has it gotten worse over time?

**Nicole Wipp:** No, it's gotten better partly because I have taken very intentional steps to manage it. I go to bed very early compared to most people. I'm in bed by which it was never part of my previous experience in life, but I have to be down in bed by that time of day in order to actually ease myself into sleep to get enough sleep throughout the night to function the next day.

**James Valentine:** Thank you. Yes we have a hand in the back.

**Jean Daley:** Jean Daley, I'm a LAM patient and I would say that the three things that have affected me most are, being short of breath when I try to exercise or try to do just about anything, particularly bending over to pick up things or do ordinary things that most people don't think twice about. The second thing would be fatigue and part of that it was related to some sleep issues because I was becoming hypoxic at night, because of the LAM, and it hadn’t been identified as nighttime hypoxia. Once that was fixed, the fatigue improved but it did not go away completely. So fatigue continues to be an issue for me.

**James Valentine:** Could you maybe share with us, maybe describe for us rather, the level of fatigue that you experience now that at least the sleeping issues have been been handled, how, can you give us an example of something that's now difficult to do? Or maybe…

**Jean Daley:** I've had to slow down. A lot. A trip to the grocery store used to be something that I sandwiched in between finishing work and making supper and now a trip to the grocery store is what I'm doing this afternoon.

**James Valentine:** Thank you. That's very very insightful. Others want to share with us their greatest burdens they have experienced? Yep.

**Karen Kinsey:** My name is Karen Kinsey and I am a LAM patient, and I would say my increasing need for oxygen is starting to really impact my life, and I'm grateful that I live here and I'm grateful that I have so much so much is accessible, but now I have to think do I have enough do I have enough oxygen in the tank to get me to from A to B to C and what if I don’t, and am I just, am I harming my heart by not being uber prepared and you know then the OCD kind of kicks in and you're like wait a minute how many tanks do I have, how much, do I have this backup cannula in case this one's broken or this tank doesn't work and so you're always trying to be prepared, which is a great thing as a Girl Scout or a Boy Scout I know, but as a, at this age is starting to get annoying to my own self as well to my husband, like oh God, really? So but I also found that once I got on oxygen at night many of my sleep issues went away, not all of them, but a lot of them went away, and I was determined, it was determined I needed oxygen at night because I have restless leg syndrome. I was like, I can't sleep my legs just won't go to sleep and my doctor was like uh-oh, six minute walk. So anyway but I thank the medical community for everything they're doing for us and and The LAM Foundation.

**James Valentine:** So I have a follow-up question for you. So you said that you have an increasing need for oxygen over time. Has that growing need for oxygen besides the burden of actually having the extra oxygen, impacted aspects of your daily life?

**Jean Daley:** Yes. I need to bring it I used to be that as long as I was an air-conditioned room with, and it was on the first floor, I didn't have to walk up steps, and there’s any type of incline, I can't do, so as long as I was in the air conditioning was perfect. I didn't need oxygen. I didn't need anything and now it's like well, I have to go to work I need to use oxygen in the car, and I need to bring it into the office, and then I need to make sure I don't run out. So, and it used to be that I just needed it for exertion, but like Mary said, when it's humid out, oh my gosh, it's just a killer, so it just is slowly, slowly becoming a more normal part of my life. The new normal.

**James Valentine:** Yes, yes. And have has having the extra oxygen been all that you needed in order to kind of maintain that new normal, or have there been things that you're no longer able to do?

**Jean Daley:** I have learned that when I go to the grocery store, I'll make sure all the perishables get put in the refrigerator and the freezer like my ice cream but any big heavy thing that can sit in the garage or sit in the basement, I let my husband take that up for me or the laundry, I'll do the laundry, but I'll leave the basket downstairs so he brings it up, and he understands, and so and now I also go to cardiopulmonary rehab several times a week to keep exercising and be monitored for my own health. So I find that that is a definitely a wonderful thing to do.

**James Valentine:** Great, thank you.

**Jean:** Hi, my name is Jean, and my daughter has LAM. She's traveling around the world right now, and I guess the biggest difference for Sarah is that her life completely changed. She was, had recently gotten married, she was diagnosed three months after that. Took a while to get the diagnosis but and she and her husband have decided not to have children, so that’s I mean, that's the biggest that I related to what you said earlier that there has to be progress of that area. But they've made that choice so as the potential grandmother that's not going to be, that's impacted my life, but obviously theirs. I think it affects every day of her life, in in countless ways, and my biggest fear as her parent, is that while she is stable now and taking, reacting very positively to Rapamune, what does that hold? I mean she's been diagnosed since she's been taking it for seven years and that's a long time and will it still be effective, and what happens next? You know you say we don't you're looking for answers of things that will not have a cure, I'm looking for a cure I'm looking for something that's not going to just stabilize my child, but help her and manage her disease in a way that you know, she's now there that say the lifespan of these people is not very long for many young women who've had this and I met lots of other LAM patients who are much older than I, and I was thrilled but most of them didn't know they had it until they were much later in life, so that's my biggest concern and that's what worries me as a parent and whether or not my child would articulate that I don't know, but she's made dramatic changes in her life in order to live her life fully now, not knowing what the future will hold.

**James Valentine:** You said that LAM affects every day of her life. Could you describe that or give examples of what you meant by that?

**Jean:** Well, like everybody else here, she has had to cut, well now she's not working because she took a year off of her life. But prior to that, she would not go to work on certain days. We live in, she lives in New York City. Subway commuting in New York can be challenging on good days, impossible on bad days. And you know the heat and humidity is outrageous so she's had to, she informed people in her office, which, even though everybody maintains that having a disability like this does not change how people look at you or affect you, it does. We all know that, and I think she's made accommodations, and her professional life has made accommodations for her. But she paces herself. There are some days she does not leave her apartment, because it's too cold or too hot. Mostly the heat is terrible. You know, there is one thing she'll do in a day rather than twelve, which is what everybody says. And I see that, how she paces herself is very different, I think. And you know. Is that because of her lung function? It’s because of her lung function which is relatively stable and fatigue. But at the same time my child is traveling around the world, and writing about it daily and I just spent three days with her in Belgium and she has more stamina about certain things that I do. So I am constantly amazed by the support she's gotten from the medical profession in this community, as well as others in this community, and I think that for a disease that nobody knew about, including myself, you know, I think it's made great strides but I think there's a very, very long way to go.

**James Valentine:** Thank you for sharing. So I know some of you listed other, something that wasn't listed. I won't call on anyone in particular, but if you have something to share just kind of reminding you that we'd be interested to hear about that. You know I started off by asking about symptoms, but I'd also like to hear about activities in life that's been a follow-up question I've asked a number of you, but maybe depending on what it is that most impacts you if you could also share with us how that has either made it so you're unable to do certain activities or maybe unable to do activities as fully as you had been able to. We'd be interested in knowing what those were that could be anything from a task around the house or on the job or that could be much bigger picture type of issue. Yes, Madeline.

**Madeline Nolan:** Well my career is teaching, I'm a gym teacher so I had to start wearing oxygen to work so these little freshmen walk in the gym and you're standing there with oxygen on, so that was an adjustment just like why would you be doing… So you had to get adjusted to wearing it in public by going out and I don't keep many secrets but that was like okay here it is, who wants to know why? So you learn to be open and to share because you want to raise awareness about things. So you had it I still work but I'm not the gym anymore, because I don't want to walk out to the tennis courts. I'm of hot humid days, or up the hill to the track five or six times a day, so now I just do health classes, so I just make adjustments along the way. And I didn't want to, but I knew okay this is opening up, I better take this, because this spot might not open up for another hundred years, and take it now even though you, I wasn't ready. I really wasn't mentally ready, so you have to change things in your life to adjust so your to your new condition and sometimes you kind of pretend that it hasn't changed. But it's subtle for a lot of people whose lung function declines. It's not like you're breathing today and the next day you're gasping, it's subtle so you just think you're getting older you know. This is what happens when you gain weight or and so no you know it's all in your head, or it's stress. No, I can't bring that laundry basket up like I used to, or bring the groceries in, and so you just, you um, you can sometimes you look back and you go oh man I used to be able to do this. So I think it's more like you feel abandoned. Like your body abandoned you, really, I took a care of you, what happened?

**James Valentine:** So was there a, I know there was a job opening, but was there something that led you to the point of looking for other jobs? I know you said it was difficult? You didn't want to have to walk to the tennis court on hot humid day. Were there other things about the progression of your disease that…

**Madeline Nolan:** Well the thing is it was progressing. Yeah. And so um I didn't want to stop working, so I just took a different position, in my same school so that wasn't, but now I'm in a classroom every day with four walls. I’m not out in the wide open space and you know, the chaos of the gym that other people don't like and they want everybody in a row and that's not my style, but I had to adjust but now it's okay because now I just teach about sex, drugs, and rock and roll.

**James Valentine:** We'll go the back and then we'll come up front. You really warmed people up with the sex, drugs, sex, drugs, and rock'n'roll.

**James Achterhof:** My name is James Achterhof. I'm the husband of Arlene up there, and I'm going to hit a couple of these things right, right here, and sort of agree but you're asking about things that it affects us and the change. Number one, more and more we have to take a wheelchair with us. She used to be able to walk anywhere and she has TS and she's 53 and nobody can tell us well, this is what normally happens at this age because we don't know anybody that has a TSC child, that's that old. Another thing is we live in a town house, and we're getting to discuss probably two to three times a week, how long can we live in this house because we have stairs, and she visits from the group home only on the weekend, but even on that that weekend and even with us both walking her up and down the stairs together, the three of us, and we’re getting to the point she's an adult and it's and we're old, and it gets more and more difficult to get up and down the stairs. The part of the thing is we that my wife said also was we worry about the seizures are getting worse and when we try to find out what can we do or can we expect this because she's getting older, nobody knows. Nobody can tell us. Nobody could give us a good solution on how to handle this. Personally, I even worry about the LAM. Does this affect her breathing, is getting, she's weaker and in a sense, it is that LAM or is that just part of the seizure thing? We also have to start thinking about, do we take the rescue med with us everywhere we go? We haven't been doing that, but maybe we have to start doing that. There's a lot of things and the doctors aren't really very helpful at all, to be very honest. So help me understand a little bit about the use or need for use of a wheelchair. Is she having difficulty, difficulty breathing? Is she more tired or she just giving up on walking? Number one, she's tired, uh, you know we like to take her out, and she likes to go places. She likes to do things, but she can't walk very far at all, and if she has a seizure and then has a problem of proceeding, how do you do that if you don't have a wheelchair. And so you know, this is changing and we don't know how to handle it.

**James Valentine:** Thank you very much.

**Lindsey Golemon:** Hi, I'm Lindsey. I have TSC and LAM. I'm going to kind of piggyback off of Madeline, I'm also an elementary PE teacher. We, I love the structured chaos as we call it. I've also noticed, I've been doing it for ten years now and when I first started I actually had a teaching partner and I have close to a thousand students that I teach, and I didn't really notice the effects of LAM, but now that I don't have a teaching partner, I'm the only certified PE teacher at my school. You know it's just me, and every 55 minutes I get a new group of kiddos. I got to set up the equipment. I might have plans to go outside. Now I don't think I can go outside that day. We have something called a moving Monday, which means for the state of Texas we have to see every kid on Monday. So every 25 minutes I get a new group of kids. It might be “boom” I got to get them outside, “boom” I got to get them to art. I got to get them to music I got to get them here and there's some days where I am just exhausted or the point where I'm like, how am I doing this by myself, and I too am worried that my education career might be going on either a change of plans or might not be able to do PE much longer, just simply because it's so difficult to not only set up equipment, it's so fast I got a new group of kids in twenty-five minutes and explain and demonstrate and so I now have to rely a lot more on my kiddos. You know, pick a lot of helpers to set up equipment, but please go get this, please go get this, please go get this. So I can teach at the same time. But it's definitely a challenge. I mean even with anything, such as even speaking and bouncing around with your kiddos, it's really hard to do and I've definitely felt the difference, just over the last three or four years. Even when I first started and I was experiencing collapses once or twice a year I might get a chest tube I'd be back at school in a week or two. I could get right back in it and I'd be fine. But now that I'm feeling my decline, it's getting harder and harder and harder to do what I love.

**James Valentine:** Thank you. So I think we're at time, but we'll take these last two comments and then we'll go to break.

**Nicole Wipp:** One or another comment I have is about the drug that were taking. I call it rapa, Rapamune, sirolimus, that the first three years I took it actually improved my FEV1 function, but now I'm one of those people that it's declining. So my fear is, is there going to be something else to add to this to make a cocktail, to help boost up my FEV1 and unfortunately I'm also one that my DLCO numbers worse than my FEV1, and no one has ever said others any there's something that we can do to help that. I mean I don't help, help, please, we need it.

**James Valentine:** Thank you. We will end with Seth.

**Seth Fritts:** So again thanks, thank you everyone for coming today. You know as I look at this list, I'd like to cover off on a couple of things. First as we, for me the priorities changed, right, it was mentioned earlier that for young adults, or as a child, the skin manifestation or the angiofibromas are some of the bigger things, and that was my case. You know is those things that when you're young you kind of stand out because you've got this kind of strange acne on your on your face, but as you get older, things like my kidneys have become obviously a much bigger priority and so you know it's things like not being able to ski as much as I used to or at the level I was skiing at you know because I was a pretty intense mogul skier and, things like karate or martial arts those type of things and so I've had to change the lifestyle that I had where I'm not able to do that as much or at least I have to be a lot more cautious as I do it. But kind of looking forward, the next things that I'm looking at, you know I'd mentioned the four tumors on my brain and given that we don't understand like the your the progression is different for every person. What that means for the future. Does that potentially mean seizures or some other kind of activity or things that I know were yet to be determined. So, I think these are all things that I know I think about a lot right now. But you know, it's things I'm sure again a lot of people are thinking about. And one other thing is this is kind of an interesting thing I've noticed with a lot of the people I've spoken to within the TS community is kind of this almost like a strange confidence issue or something like that when you're younger where you're always feeling like you're hiding something because you know you have this rare disease and you don't really want people to know about it. Because you feel awkward and I didn't think anything about that until I really started joining the TS Alliance and working in the community is you hear people talk about how they're there kind of feel different and that's just something that growing up I remember I always had like this kind of confidence issue and then as you get older you kind of realize okay I just have to deal with it, but now I think that's something that a lot of people deal with. It was important as important. Yeah.

**James Valentine:** Thank you. So I think we’ll take a break and come back at 3:05, so quick refreshment and bio break, everyone.