[MUSIC PLAYING]

[CLASSROOM DISCUSSION]

FRANK SCIURBA: So today we're going to talk about mainly bronchoscipic approaches. Mark would like me to give a definition of precision medicine, so we'll start out with that.

All right, so, Mark this slide's for you. You might want to watch it some.

[LAUGHTER]

Thank you. So precision medicine actually-- so it's a term that's been adopted by the NIH. It's been modified and interpreted in many ways and this is my interpretation today. Originally, it was designed really to deal with unique molecular aspects of an individual that will allow us to precisely target therapy at the right time for the right person. And that was the program that Barack Obama funded in 2015.

There's been a lot of controversy, and Mike Joyner, in JAMA, has written a lot of publications as to whether this is possible, whether we've made any progress despite millions of dollars being generated in that direction. The idea is that there will be unique progression of phenotypes related to physiology, imaging, comorbidities linked, and driven by basic molecular cellular mechanisms that will be predetermined and unique within individuals. And that concept inspires something that we began observing ever since we looked at hundreds and hundreds of CTs in the original [INAUDIBLE] reduction program back in the '90s, and which stimulated the original SCORE grant that used variation in imaging and physiology to try and define molecular aspects of genetic aspects in COPD.

And we're motivated by the fact that these two individuals defined by the traditional FEV1 actually looked extremely different when you look at their imaging. This person having relatively little emphysema and ultimately airway dominated process verses this person that has really complete parenchymal lung destruction. And it stimulates one to think, there must be differences. And we were able to quantitatively describe those differences in measuring quantitative wall area thickness of the airways versus low attenuation emphesyma.

This is in collaboration of Vancouver. And there were individuals that had predominant airway thickening and those predominantly emphysema had similar lung function. Those that had both abnormalities had the worst lung function. Those with either abnormalities had pretty normal lung function.

Jessica summarized our experience on her first fellowship publications. And of course, probably not everybody has-- in the room-- has seen my confuseagram, but this basically describes the chaos and understanding. Any individual patient that comes to you in the clinic may be in any of these spots where airway and emphysema processes may differ, but also the degree of pulmonary vascular disease. And as you'll see, things that appear at one time can be irrelevant. Like [INAUDIBLE] collaterals and osteoporosis relative to COPD can vary significantly in these individuals.

And so, part of the aims of the SCORE, and then ultimately in helping to write actually, the RFA [INAUDIBLE] and making the changes [INAUDIBLE] write the grant for COPD gene, the goal was to try and classify these patients into unique clusters and subgroups. And so multiple different approaches. Cart, various classification analysis-- tried to sub-classify these patients. And ultimately, across multiple publications, we've learned that even though we can classify withing the data set, these are very often not reproducible across data sets.

And so, to this point, we failed in finding discrete subsets of patients. But what we have found is traits that vary significantly across those individuals-- degree of emphysema, eosinophil levels, et cetera. And that perhaps targeting the specific traits, and not groups of such diseases may be the way to go.

And so, the ideal goal of precision medicine or personalized medicine would be to go from this scenario-- this is for Faraz-- your favorite slide you say--

AUDIENCE: It is my favorite slide.

FRANK SCIURBA: --is going from this concept, where we're just looking at the mean change in these groups, and whether that's moved, to be looking a little bit more granularly at the groups that go-- these are the exact same dots now colored. And we want to try and avoid doing the intervention in this group. These are the home runs that are likely cost effective. These folks here don't do anything, and the yellow dots you would have to do a cost utility analysis to determine whether you want to do that.

And so the more we can subclass by those individuals and target specific mechanisms, the more likely we're going to get the right color dots going here. So there actually is one subtype of COPD that we have been successful, and of course we all know the endotype, which we guess the phenotype [INAUDIBLE] deficiency. And in this process, over time, this is what we can do with quantitative CT analysis. It's a density histogram of each [INAUDIBLE] on the CT scans. And over time, in emphysema, the density shifts to the left.

Well, there were two clinical trials and then a meta analysis of these two trials together. We documented with [INAUDIBLE] replacement therapy, we can significantly slow this shift to the left. So this is an example of what we like to do across the other 98% of patients who have COPD. So we did this trial a couple of years ago, where we-- taking an example of a successful drug in asthmas, learning that in fact there are TH2 mechanisms involved in COPD, we did IL5 modulation in a clinical trial-- two sister trials in COPD.

And while there was a 20% reduction in exacerbation rate in this group, one being significant the other borderline insignificant. In fact, the FDA, and probably appropriately, felt that the effect was not significant enough to approve a biologic in this disease. On the other hand, if you look at a subanalysis stratified by your eosinophils, we find that in fact those-- peripheral blood, the eosinophil level, the eosinophil level we get from ordering CBCs for forever and ever, that we generally ignore in the labs, as that goes up and even at historical level of 300 or more per microliter now begets 36% reduction in exacerbation rate in the treatment group.

So we're progressing, at least, in that direction by identifying a specific part. But not really a home, or dramatic. In taking the lessons from asthma, we're currently doing clinical trials of IO4 receptor modifications, [INAUDIBLE], and we'll see whether we can succeed there. But targeting other mechanisms, traditionally thought to be important to COPD, generally TH1 type responses has not been overwhelmingly successful. We were involved, a number of years ago, in an anti-ILA, which missed its primaries.

Although there was a minimal shift in this [INAUDIBLE], that company went bankrupt. TNF-alpha modulation seems to make sense, mechanistically, from what we understand in COPD. A couple of clinical trials have been negative.

IL-1 beta and other major Th1-type cytokine, canakinumab, failed and COB. Whether we're not targeting the right subgroup, or not selecting the right outcome measures, is a big question with these trials. But nonetheless, so far, we have failed. And then, IL-17 modulation-- that trail is completed, I think about three years ago now. And somewhere the date is buried. I suspect if it was a home run, that we would know the results of it. I suspect it's a negative trial.

And so, that's the concept of precision medicine as we've traditionally thought. Can we target specific molecules that allow us to change the course of disease. On the other hand, we've made an argument that using less traditional definitions of precision medicine, using device intervention based on unique sub-phenotypes, we actually have made a lot of progress. And I would argue, short of the progress in cystic fibrosis in these subsets of individuals who can respond to these therapies, we have had some of the greatest impact from these interventions.

So, I'm going to discuss interventions in the emphysema dominant, and then progress to what we're now beginning to study in airway-dominant disease. So, this all started with a patient bringing a Reader's Digest to me, and telling me there's a surgeon in St. Louis who is cutting lung out in patients who we would never even send for cancer reception, they were so severe, in that they were doing better. And, of course, my response was, that's crazy. And then I found out that [INAUDIBLE] had already done a couple of cases here in Pittsburgh-- and said, you know you can't do that unless we're studying it because this is just such a counter intuitive concept.

On the other hand, it's now actually somewhat intuitive, in that, if you take out giant areas that can't inflate and deflate-- that take up space in a limited thorax-- and actually resect those areas that are actually often compressing relatively normal preserved lung that cannot expand and deflate within that limited thorax-- that in fact, you can not only decrease the residual lining that you can rearborize the vessels and now allow more functional lung to participate in the ventilation process.

So this is the schematic of the major fissure in that individual which now has changed position and allowed expansion of the previously compressed lung. We documented, in fact, and this is a normal pressure volume curve. These are the two patients-- two examples of patients that we did. One soft gel balloon and one elastic recoil study, showing after the procedure we can move back toward normal in the pressure volume response of the lung.

So basically, the NIH decided that this needed to be studied. We did broad enrollment in the national emphysema treatment trial in the late '90s. And the first thing we found is that there is a subgroup of patients, the more severe patients, with homogeneous disease-- often represented by very low DLCOs and FEV1-- who had a very high mortality rate with this procedure. This was the first publication headline-- Patients at High Risk of Death After Lung Reduction Surgery-- which pretty much shut down [INAUDIBLE].

If you don't read anything else but the title, you would never want to refer a patient for lung reduction surgery. We had a hard time recruiting for the other 90% of the patients that actually did have these extreme phenotypes. But in the end, we did complete that trial. And this is a sub-analysis of what we identified. We wrote the exercise protocol for this net trial, which wound up being along with upper-lobe and homogeneous distribution of the disease, two stratifying phenotypic parameters that describe subgroups of patients who are going to respond.

So patients who had upper-lobe dominant disease and poor functional status had a significant improvement. This is a composite endpoint of mortality, or two times the minimal difference of quality of life deterioration. Significantly greater composite death rate in the control group versus the surgical group. Whereas those patients that did not have these two attributes, did not benefit from the procedure. So ultimately, CMS approved this procedure and as it stands today, in upper-lobe dominant patients, particularly those with low exercise tolerance.

Since we published these in 2002, ultimately there's been almost no referrals. This is the number of referrals in the thoracic surgery database-- generally in the low hundreds range, up until recently to that point. And often it is the fact that these folks have to go. They're very sick. They have to go through major surgery. This with a net-- non-high risk mortality rates-- this was the subsequent data in the thoracic surgery database. On top of that, up to 20% of those patients after the surgery have prolonged stays, including readmission and other complications to the procedure. Many of them do extremely well, but it's a lot closer, and really, the referral rate reflects that.

So as a result of that, we worked with some startup companies who had some ideas and helped to develop these technologies that would elicit the physiologic response to the surgery, but hopefully with less complications and mortality rate. And the two products that are currently FDA-approved, as of last year, are the valve products. One is the Zephyr Valve, which we are using here, which is an intact flat valve placed to occlude a lobe. The other-- which Brian and I currently have approval to do in a persistent pneumothorax, but haven't used it for emphysema-- is the spiration valve. Both with Nitinol frames and silicone covers that act to occlude a lot of the air out, but not to return into a specific lobe.

So, the concept is similar to lung reduction. We place these valves, allowing a hyper-inflated lobe to collapse, allowing expansion of the ipsolateral, better-quality lobe, and also reducing the residual volume improving respiratory muscle mechanics.

Things we learned in the course of this trial. So, I was the PI of the initial pivotal trial, published in 2010. In this trial, we learned that patients who were the most heterogeneous-- the greatest difference between emphysema and the targeted versus ipsolateral non-targeted lobe-- actually did have clinically important improvement in FEV1 and six minute walk distance, but very little response in those patients that were less heterogeneous. The study was not explicitly designed to prove the subgroups. And the FDA did not buy it. And therefore, did not approve the product at that time. So, that company went bankrupt. It was bought by Pulmonx, which is the current company.

But we learned a couple other things in the course of executing that trial. We learned that it matters if the fissures are complete. And it matters if the valves actually completely occlude the lobe. And it winds up, about 35% of the patients actually didn't get an effective intervention to the collapse that lobe. And this is an example where if you put the valve in too deeply and you have an open segment, there's no chance for that lobe to completely collapse and [INAUDIBLE] effect.

And so, something that was just an anatomic curiosity, now becomes very important. Whether the fissure goes completely from the hilum to the plural surface, and whether there are connections between the upper and lower lungs, all of that affects whether the targeted blow can collapse. And somewhat more than 50% of patients will have a complete fissures, but that means that about 45% can not have the procedure. And a sub-analysis from that [INAUDIBLE] trial showed this is the result of a lobar-targeted lobe collapse in the overall [INAUDIBLE] trial. And these are the patients who we visually identified complete fissures, nearly double the lobar collapse [INAUDIBLE] drives the beneficial effects of this procedure.

There was another technique that was more of a curiosity and was available. And we applied to this technology to identify now-- physiologically in the bronch lab-- patients who have lack of physiologic collaterals. And basically, this is the flow out of the targeted lobe. We inflate a balloon and continue to measure that flow. If that flow goes down to zero, that means there's not ongoing supply by an incomplete fissure from the ipsolateral lobe. In this case, the fissure is not intact. Collateral flow continues.

And this person would not likely get lobar collapse. This is a spontaneously breathing individual where the inspiratory pressure also goes up, although now we're doing the procedures in ventilated patients and we just look at the expiratory flow. This is a case that Brian and I did where we first assessed the left lung. And as you can see, over four minutes, there was no drop in flow after balloon inclusion of left lobe. On the other hand, the right-- you can see that the flow gradually deteriorated to nothing. We put both valves in this person and the lobe collapsed, and the person had a beneficial effect.

So based on the findings from the [INAUDIBLE] trial, Dirk-Jan Slebos and Karin Klooster in Groningen, Netherlands performed a single-site study using the Chartis device and got dramatically greater results in lung function. Nearly a liter drop in residual volume and four times the minimal difference improvement in St. George's Respiratory Questionnaire in an occlusive, attempted blind study. But along with this improvement, they also increased their pneumothorax rate to actually over 20% in the details in the paper.

And consequent to that single center study, the technology was purchased a pretty cheap price by Pulmonx, who then proceeded with the LIBERATE second pivotal trial. In this trial, 190 patients were randomized. We used the Chartis device and only inserted those patients with no collateral. We confirmed that with a 45-day post CT scan that in fact the lobe was completely occluded, and if it was not, the valves were repositioned. And then, subjects-- because of the pneumothorax rate, to prevent a mortality rate, which occurred if patients were discharged directly from the hospital in several cases-- were admitted to the hospital for five days to monitor their pneumothorax.

These are the primary result of LIBERATE trial, which is the proportion of patients that had at least a 15% improvement in FEV1 was 48% [INAUDIBLE] values versus only 17% in the Control group. The characteristics of these patients-- so you know the targeted lobe had based on the quantitative threshold about 71% emphysema. The FEV1 was 28% predicted, and the residual volume was about 235% predicted. So these patients were fairly hyper-inflated. And these are the primary and secondary outcome measures. All very significant and much more significant than in the original [INAUDIBLE] trial before we documented absence of collateral flow.

So the other downside of it, though, is that with this more effective therapy, we now got a significantly higher pneumothorax rate with 27% of the original 45 day treatment period, and about 6% afterward. The timing of those events as you can see, were very, very likely to occur in the first three days. 75% of those events occurring in the first three days, and the majority first five days, with only one mortality due to pneumothorax of all the other discharged patients after the first five days. So this is the reason why we admit these patients to the hospital and receive some of the preliminary results that we've experienced.

So the question is, what are the results of this valve procedure compared to the net trial? Well in the LIBERATE trial, these are the responder rates based on the published minimal important differences of FEV1, RV, walk and St. George's Respiratory Quality of Life Questionnaire. And they're actually pretty similar. The responder rates to valves are not that dramatically different than the surgery, without nearly the associated morbidity. So, as a result of these FDA approvals, CMS, we got a a pathway for reimbursement. We presented this to the Technology Review Committee here at UPMC, the TFAB committee, who has given us permission to do 25 cases out of the gates.

So our team has regular meetings. I often do a pre-screen with Natalie, but ultimately, Jessica, Craig and Roy are involved. In some of the cases, particularly borderline cases-- and in those cases we consider for lung reduction surgery or transplant-- we do a preliminary review with Carl Fuhrman and Pablo Sanchez every month or so. Procedures are done under general anesthesia. Originally, we separated the Chartis evaluation because we didn't want that emotional-- when they wake up, basically, did I get the valves, didn't I get the valves-- but for a variety of reasons, we now combined it.

Before we confirm absence of collaterals just based on fissure integrity, we put the folks under general anesthesia, do the Chartis evaluation. If they are Chartis negative, we then proceed to valve insertion. Patients are admitted five days, four overnights, to 10D/10G. And our results, so far. We have done 21 Chartis cases. Six were collateral positive and could not proceed to valves. Incidentally, we've had a much higher success rate than the LIBERATE trial. All but one of our patients had complete lobar atelectasis. Associated with that, since we've effectively resulted in atelectasis, there's about a 50% pneumothorax rate.

I have to say that 10D/10G has a incredible job. All of our physicians and, of course, our extenders up there, and the nurses-- it's a fire drill when one of the patients have an event and they've all been very effectively managed. Three cases we could not re-expand the lung and the valves were removed. There have been no deaths. Only two patients have had six month follow-up. One was a patient of mine, who, if I didn't know the family very well I would not have done it, but it was fully understood. And she actually went from home hospice outpatient rehab and is doing very well. Second patient at UB1 went from 34 to 61% [INAUDIBLE] so this can really work in the right patient.

So let me just give you case. 67 year-old patient with COPD, other co-morbidities, a long smoking history. [INAUDIBLE] showering progression over four or five years. On triple therapy. Still symptomatic despite rehab. Some low flow of supplemental oxygen. FEV1 was 43% predicted with hyperinflation of 192. Relatively reserved EL of 42% predicted. Clearly heterogeneous upper-lobe dominant, with relative reservation of the lower lobes. Both on coronal, axial views here and here's the sagittal views. Interestingly, the right one-- this is the lower lobe. We worry about these because if we collapse that, the stress of [INAUDIBLE] negative pressure on these blebs can increase the risk of pneumothorax.

Fortunately, the left side was collateral negative on Chartis and we proceeded with that insertion. The company provides this service where we can load the scans-- upload the scans and they give basically a schematic. We always look at the scans, and we don't always agree with it. But it is a nice little summary of quantitative visual fissure completeness. Generally if it's greater than 95%, the Chartis is also going to be negative. If it's less than 80%, the Chartis is almost always positive. And we'll always do the Chartis if somebody is at least over 80% visual fissure completeness.

This shows two density thresholds and the percent destruction in the upper lobes versus the lower lobes. In this case, we targeted the left side. Clearly a greater heterogeneity on that side. 94% fissure completeness. These are the lobar volumes which are also given by the schematic. In this case, three valves were placed in the apical posterior, anterior, and lingular segments and had an effective volume reduction on that side, with elevation in the left-hand diagram. Again, we've seen this and all but one case and actually, we haven't had a follow-up since discharge. So that case we're hoping will also be effective.

Another case. 62 year-old woman. [INAUDIBLE] history. Severe dyspnea on exertion. FEV1 35% predicted. RV, though, is less than 175. It's 163. With a particularly low DLCO and very high oxygen needs, particularly with exertion. This patient would not be a candidate because of the lack of severe hyperinflation. Echo showed an RSVP of 51. You're not going to get symptomatic improvement if the predominant thing limiting your patient is not lung mechanics. And we believe this person is most likely limited to pulmonary vascular and gas exchange abnormalities. We referred the patient to-- just a plug for our vascular folks. They have an ongoing trial with inhaled treprostinil and I will refer patients who have secondary pulmonary hypertension for this program. As I hope many of you would. Also this person would be considered for organ transplantation, they have the criteria.

So how about patients that are collateral positive? And suppose they are even homogeneous. They're not going to have options for lung volume reduction, they're not going to have options for valves. What are their options? So this led to the development of other technologies. One of which we have already vetted. That's lung volume reduction coils. There were three sizes of coils. 10 to 14 inserted bilaterally, with the concept of going in straight and then folding up like a baseball. So, folding in half, folding in half again. Rolling in the lung, compressing the lung tissue, and thus being collateral flow independent.

We published this a couple of years ago in JAMA, but it ultimately was not approved by the FDA. [INAUDIBLE] rationale yet. These patients were more hyper-inflated than patients in the valve trial. The BODE index-- which is one of the parameters used in the allocation scores for lung transplantation-- about a third of these patients were qualified where they are other [INAUDIBLE] et cetera, [INAUDIBLE] lung transplantation.

In addition, these patients, as opposed to our priority for valves-- the vast majority were homogeneous rather than heterogeneous. So these are the primary results of that trial. While all primary and secondaries were statistically significant, the clinical impact was felt not to be significant enough for the FDA to approve it. So it was only a 10 meter difference in walk distance. Only 3.8% change in FEV1. There was significant symptomatic improvement, but it was not a blinded study. Ultimately, the FDA chose based on those results not to approve it. But as you can see, there were individuals-- this is the coil group, this is the response in each metric versus the control group in the right panels. And you can see, definitely a shift in some individuals. So again, were their characteristics that identify these individuals that had-- this is the symptomatic, a drop in this score is good-- that were these respondents.

One other thing we learned-- as with the valves-- we learned that fissure intactness was important. That individuals who had characteristics that would result in-- what at first we thought were pneumonias, but ultimately were necessary for the coils to work-- would be to develop an inflammatory response and what we call coil-associated opacities. Which, we had begun to really sort out.

Other things we found-- the patients that were the most hyper-inflated, in particular, had the greatest response compared to those that were less hyper-inflated. And other characteristics that ultimately inspired the elevated clinical trial in Europe to begin, including visual absence of airways disease, substantial emphysema destruction, again particularly hyperinflation. And we learned-- again, like with the valves where you have to position the valves right or it's not going to work-- that when we use densitometry to target the lowest attenuation lobe, that we got the best results.

So this trial was designed. My European colleagues, while blinded, suggested that some of the patients were doing remarkably well. Ultimately, the company decided to abandon the technology. We could probably pool our spare dollars and buy it if we want, and gamble on it. But for right now, it's out.

On the other hand, this is a technology that died [INAUDIBLE] years ago, that has been tuned up and is now coming back. And it's likely a trial that we'll be doing in the near future. And I call this the cappuccino machine where this is basically steam, and we'll blade the segments that are most emphysema-- we can now target this. And using some of the newer navigational bronchoscopy techniques, can actually target specific regions of emphysema. And they're using those approaches now. And actually have gotten-- while they're in the early stages, there were some significant injuries-- a couple of patients had an ARDS response. We certainly wouldn't want that. But, significant improvements in FEV1 across the board.

So this is, again, refinement in these technologies in selection and approach are allowing them to actually have an impact.

AUDIENCE: How does that work?

FRANK SCIURBA, MD: So basically, a thermal water steam is bronchoscopically delivered through a catheter to areas of the greatest emphysema. Results in peripheral airway fibrosis and collapse of the emphysema [INAUDIBLE] beyond those peripheral airways.

So we showed you things we've done for emphysema. How about the other phenotype? I've never done one of those and when the company approached us to do them 10 years ago, I said try it on a few other folks first. They've gotten a convincing argument at this point, so we'll look things over and consider it.

So we've got now some approaches we've progressed for emphysema. How about those patients that have low FEV1s, who have a high exacerbation rate, who have cough sputum production, they're more airway-dominant phenotype. Do we have anything for them. And so, we're currently now starting an international clinical trial doing targeted lobe denervation, where we deliver an RFA heat signal with the intent to decrease the chronic parasympathetic tone, which all our drugs are directed to currently in treating emphysema. And also with the hopes of blunting the airway hyper-reactivity which is present and documented, although less appreciated in COPD as well as asthma.

So basically what happens is, there's an RFA-- cooling catheter that protects the epithelium in the cartilage and provides a heat signal on the surface of the airways that [INAUDIBLE] the vagus nerve, which run along the surface of the airways bilaterally. So these are some of the pretty clinical work in rodents, in a ovalbumin induce and a [INAUDIBLE] sensitized model, showing that with nerve ablation you can significantly decrease the responsiveness to a histamine or a methacholine response. So the concept is not only ablating efferent nerves that supply the muscles, but also the afferent pathways mediated through the parasympathetic ganglia. Ultimately, the brain stem, which trigger the efferent responses should be ablated, both with respect to bronchoconstriction and smooth muscle, but also mucus secretion.

In addition, the vagus nerve secretes neuropeptides and other mediators besides just acetylcholine that may have an impact. This is the design of the device. It's delivered through a large bronchoscope at 3.1 millimeter channel. It's a balloon that's inflated. It has an electrode on the surface, and a coolant that goes through this channel that-- again, prevents-- we don't want to burn a hole through the airway. So we cool that thelium and cartilage, and ultimately, the tissue-destroying heat signal then emerges on the surface of the airways and ablates the vagus nerve. Here's the slide that I put earlier.

This is just a model in some gel, of exactly what happens. Showing the heat signal protected at the surface of the electrode, but then delivered at a point where the vagus nerve should be. This is just a quick cartoon to show the procedure. It goes way too slow. Basically, through a large, or 3.1 millimeter, this is the plated electrode. The coolant runs through there. The heat signal is delivered. Again, the coolant protects the epithelium and the airway and results-- we do it in four 90 degree segments. It's a little more complicated because we don't deliver it if the esophagus is right behind where we would deliver the signal, because we don't want to ablate the vagus nerve to the stomach. Gastroparesis was a problem early on, and we have learned to avoid that.

So with four activations in each lung, we treat both lungs at the same setting. These are pNM staining of the axonal fibers in a sheep model. And about 50% of the distal fibers to the point of treatment are destroyed. And also it results in decreased physiologic hyper-responsiveness in these sheep. They've done-- compared to about any other device company I've worked with, they have the best preclinical research. And also, they've done really nice clinical development with feasibility, optimization, and actually developing a new catheter and new strategies. And ultimately, just published this double-blinded randomize, which is very unusual for device intervention in phase two-- 82 patients in Europe and Australia. And the results of that trial, [INAUDIBLE] trial, show that.

So this was designed as a safety trial and winds up, the safety signal could be converted into an efficacy signal. Basically, individuals with COPD exacerbations [INAUDIBLE] and all caused respiratory events were lower in the treated group than in the sham group. And these patients were blinded, as well as the investigators, to the procedure. If you look at hospitalizations in this trial, and moderate to severe exacerbations, while not powered for this there was a significant reduction. And this inspired the primary outcome in the phase three trial moving forward.

So this is the Airflow 3 Trial that we're currently performing. It's a multicenter international trial. The key inclusion criteria-- this is a hard trial to recruit for. Patients have to have at least two outpatient treated or one hospitalization exacerbation. The physiology range is typical. They have to be symptomatic, and they have to have record documented treatment with both a LAMA and a LABA, and anticholinergic and beta agonist for at least 12 months. Ultimately, the primary outcome is going to be the exacerbation reduction.

So the last technology I'm going to tell you about is the redox electrocution study that some of you know that we are doing. Where a low current, high voltage is applied across the surface epithelium, probably penetrating to the submucosal lands and to some extent, the smooth muscle. This causes, basically, a hyper-electroporation that results in the cells losing their polarity and falling apart in a non-inflammatory way. The mucus glands and epithelial cells-- we try to touch everything that we can touch with this little catheter. It can get very thin and wide, or very long and skinny, to go down to the fourth and fifth level bronchi.

And basically, the histological documentation is that this epithelium regrows in four to five days. This is just an anecdotal example of typically what we see when we select these patients. This thick bronchitic mucus. And when it works, we see the nice serous secretions in follow-up. We do one lung, and then a month later, treat the opposite lung. The histological studies done in the European and Australian patients in the phase two trial-- 54 lungs showed-- they did a blinded mucus scoring and showed about 39% reduction in goblet cell hyperplasia in these individuals.

In addition, significant improvement in the St. George Respiratory Questionnaire. This is the CAT score. CAT 2 points is considered clinically noticeable. SGRQ 4 points. And you can see pretty dramatic reductions in symptoms. This was unblinded, so it has to be taken with that consideration. As we move forward with the double-blinded trial.

The CAT has-- the first two questions in the CAT are 0 to 5 cough and mucus. You can see this is the CAT cough score, and the phlegm score before treatment. And these are the scores after treatment. You can see at three months and six months. You can see pretty dramatic effect. I mean, I can tell you, patients that are still coughing-- and if they try and tell you that they're better, their relative pretty clearly tell you, no, I'm still not sleeping. So you know, these things all have to be proven in double-blinded trials, but it's promising initial results.

There is some objective data and we have the histology data. These are the 54 cases with quantitative CT analysis before and afterward. This is one case example showing increase in accessible quantifiable airway volume after the treatment in these individuals. So again, some objective information to support the symptomatic improvement.

AUDIENCE: Frank. Real quick question. Any changes in mucociliary clearance for these patients?

FRANK SCIURBA, MD: Yeah, good question. I don't have the answer. But you know, so Tim and I actually submitted a [INAUDIBLE] to the group, that they may let us do it in a few patients although initially it hasn't been funded. Alison is funded to microbiome on the Airflow 2 patients [INAUDIBLE] Alison Barber.

So the concept of precision and COPD is that, if we look at parameters besides just the FEV1, their heterogeneity, the collateral, or whether the magnitude of emphysema. We can begin to actually select patients that can effectively respond. And just to put in a plug for the biologic and device clinical trials currently ongoing, there's unique differences between these trials and their inclusion. Three of them are exacerbation reduction trials. The dupilumab, the tezepelumab trial. And then the targeted lobe denervation trial. The dupilumab trial-- one of the key inclusion is the eosinophils of greater than 300. These patients all have to be on documented medications. I mean the FDA is not really keen on approving these more complex therapies on individuals that are not optimally treated.

This is actually a big breakthrough that I'm kind of proud of is, you know, battling and discussing with the FDA and we've convinced them for the first time to use a PRO, the CAT score in assessing and regulating the redox therapy. So this will be the primary outcome in the Gala trial moving forward.

So last case is a 71 year-old, 70 [INAUDIBLE] history. Former tobacco smoker. Three outpatient steroid tapers in the last year. On triple therapy for at least two years. Has a CAT score of 20. The highest CAT score is 40. 10 is usually considered symptomatic. Completed pulmonary rehab. Has an eosinophil level 327 microliter. FEV1 39%. RV 220. Relatively preserved DLCO. Not on oxygen therapy and has only visually mild emphysema as supported by this sagittal CT image.

What therapeutic options are available? Well, we do have Roflumilast, which causes blasting diarrhea in about half patients that have tried the treatment. Very few continue on it, although the diarrhea does abate somewhat over two weeks if you can convince them to continue on it. In the end, it only results in about an 18% and 20% reduction in the clinical trials and exacerbation rate. Patient had a problem. That doesn't work, Azithromycin, we proved in the COPD clinical research network, can work. But that tends to be most effective in more mild patients.

This patient was enrolled in the dupilumab trial and so, consider that. You get the [INAUDIBLE] eventually going to cost even after the supplement, thousands of dollars. You could prove whether it works or not. What if her eosiniphil level was low? She wouldn't qualify for dupilumab trial. And the patients wanting in the cardio lung [INAUDIBLE] trial, so please consider us with those [INAUDIBLE]

So in conclusion, we have made progress toward a more precise clinical classification and this is really the critical step to be able to do more precise treatments. I think I've shown that with this more precise clinical classification, identified traits-- that were thought perhaps not even to have been important-- we've now developed effective emphysema treatment, and we're working toward developing a device invention for airways disease. So. Thank you for your time.