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TRANSCRIPT - GR 03 14 25 ***"From the Bench to the Bedside: Investigating the Impact of Type 2 Immune Blockade on COVID-19 Outcomes"*** guest speaker Jennifer Hendrick, MD, University of Virginia

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Internal Medicine Grand Rounds

- All right. Thanks, everyone. Welcome to medical grand rounds. We are delighted to have Dr. Jennifer Hendrick with us today, speaking on from the bench to the bedside, investigating the impact of type 2 immune blockade on Covid-nineteen outcomes. I'll take us through our Cme disclosure slides, and then Chief Resident Dr. Hasan will introduce Dr. Hendrick
- Alright, Dr. Hendrick's presentation objectives
- for faculty claiming Cme. Credit. Grab a photo of this screen here. But you'll also get an email with the code shortly.
- All right, Dr. Hasan. Over to you.
- All right. Good afternoon, everyone. It is my distinct pleasure to introduce Dr. Jennifer Hendrick as our grand round speaker for today. So a native of Rochester, New York, she earned her medical degree from State University of New York Upstate Medical University. She went on to complete her internal medicine Residency, infectious disease, fellowship here at Uva, while also obtaining a master's in clinical research. She's now an assistant professor in our division of infectious disease and international health.
- Her initial research and clinical interests included enteric disease and global health working with Dr. Petrie during her residency to study Cryptosporidium in a cohort in Bangladesh, focusing on the cell, mediated immune response to infection.
- With the beginning of the covid-nineteen pandemic at the start of her infectious disease fellowship. She shifted her focus from gut immunology to lung immunology, investigating epitopes of interest in acute covid-nineteen infection.
- In this space Dr. Hendrick designed and executed a phase, 2. A randomized control trial investigating the use of Dupil. I'm going to say this incorrectly dupilumab for the treatment of those hospitalized with covid-nineteen. She also conducted a follow up study exploring pulmonary dysfunction, as it relates to acute, immune response. During covid-nineteen we're very excited to have to hear more about her work from the bench to the bedside.
- So please join me in welcoming Dr. Hendrick.
- Hi, everyone alright.
- So. Thank you, Shaina, for that introduction.
- I'm going to be chatting and thanks for inviting me to chat about what the Petrie Lab and I have been up to for the last couple of years in Covid-nineteen research. Specifically the type 2 immune response and its impact on covid-nineteen outcomes, I'll say, for the residents in the room. I started this project in spring of 2020. I was a 3rd year resident here about to start id fellowship. So a lot of the work you're going to see in here are, as a result of a lot of really just the brilliant scientific minds, collaborative minds, the creative minds of of people here at Uva, all of whom

are my mentors. So I'm really just the one telling you about the work. But it's really just a group effort of a lot of people. I've learned a lot from. So we'll start at the beginning. And this is initial data from our biorepository here at Uva. So for those of you that don't know. At the start of the covid-nineteen Pandemic Bill, Petrie and Judith Woodfolk organized a biorepository of covid-nineteen samples, and these were patients that had otherwise had clinical absent like Cbc Cmps. And this was residual serum that was left over from these samples that we stored for research purposes. So as a result, we had a lot of biospecimen, a lot of opportunity to study covid-nineteen. And this was kind of the initial. The initial finding that sparked us down this path. And so this is the work of Ali Donlin, who is a Phd. Student in the Petrie Lab, and is now works at Fred Hutch in Seattle.

- And really, this came out of a principal component analysis, which is a nice way when you take a large amount of data which in this case it was taking serum samples from Covid, positive and covid negative patients and looking at close to 50 cytokines, chemokines and growth factors, and seeing which is the most important, which is the one that's most determinant of covid-nineteen infection and severity, and Il-thirteen was one of the top markers identified Il-thirteen functions in a lot of different ways, but you can really think of it in the atopic world. So allergic diseases. So it recruits eosinophils, M. 2. Macrophages. It functions in mucus secretion, in the airways proliferation of smooth muscle and fibroblasts. It activates fibroblasts. And that's important for fibrosis and collagen deposition. And in this case, we're really worried about the impact in the lungs.
- So then, when we looked further at Il-thirteen and its associated association with clinical outcomes from COVID-19, we saw that those who had lower levels of Il-thirteen.
- Those who had in the higher tier of Il-thirteen were more likely to be 2.7 times more likely to be intubated for their covid-nineteen disease compared to those who had lower levels of Il-thirteen, and that was adjusted in a Cox regression analysis for age, sex, and comorbidities.
- This was also a. This was also seen in another cohort. This is a cohort out of Yale that had looked longitudinally, longitudinally at its covid patients, and that was they separated out their patients into severe disease and moderate disease, moderate disease being those that require the basically hospitalized. But were 4 patients, severe disease being Icu patients, and they compared it to healthy controls. And among many cytokines that were that were elevated, they did see a trend soar towards type 2 immune response. And so they saw a significant elevation. In Il-thirteen over they looked out to 2025 days into infection.
- So Dr. Dolan, in the Petrie lab went and was kind enough to take me down to our Bsl. 3. So this was a lot of mouse work that was done down in the Bsl. 3. That is still being done down in the Bsl. 3 that was looking at K. 18 ace. 2 mice that were infected with Covid-nineteen, and we saw a difference in survival of mice that were given Il-thirteen blockade. So an anti il-thirteen antibody compared to a control antibody, they also had reduced clinical scores and looking further into those into those mice, we found that through Rna-seq analysis of the whole lung we saw the most downregulated gene in the Il-thirteen neutralized mice was has. One has stands for hyaluronan synthase, which is interesting, that encodes an enzyme that produces hyaluronan. That's a component of your extracellular matrix. It normally, exists in. You can think of it in airway epithelium, in the endothelial cells of the

vasculature and upon injury, particularly when we're thinking about the lungs. It is leaked into the alveoli and airways.

- So then, further, in this mouse model, so the top, those top pictures there are from the mouse model, and these are lung histology we saw everything in green is stained with Hyaluronan, so we see all the way over on the right there the uninfected patients. You can see the hyaluronin that's around the airway and the vasculature. If you look in the infected mice, you see it everywhere, it kind of leaks out into the space. And then, when you see the mice that were neutralized with Il-thirteen, you see that effect diminished.
- This was also seen in human autopsy data, so these are the bottom rows are Covid-nineteen positive patients compared to covid-nineteen negative patients, and you see evidence of Hyaluronan in the lungs, which is not really seen in covid negative patients, although you can see Hyaluronan in other pulmonary diseases. So it's been implicated in asthma and Ild and things like that so this is a recent publication from collaborators of ours over in Manchester, Judy Allen, Rebecca Dodd, and Tony Day, who who are also working on this process of Hyaluronan deposition in the lungs. And what all, what are all the the chain reactions that leads to this? And and how does this lead to pulmonary dysfunction that we're seeing. So picture, there are your are your Hyaluronan. So there's a light chain in the heavy chain link the heavy chain in purple, and you see that a lot of different associations with things have yet to be discovered. But the idea is that Hyaluronan leaks out during injury, leaks into the alveoli into the airway space. And it's essentially like a chemo attractant for immune cells.
- Which is interesting when you think about long covid right? and so we'll get into that further. So we then looked at, we looked into the large databases. So we looked at, how do you block Il-thirteen in humans? Dupilumab is a drug that blocks Il-thirteen. It specifically blocks Il-four receptor Alpha, which is shared by both Il-thirteen and Il 4 2 big cytokines for type 2 immunity originally approved in 2017 for atopic dermatitis, and has since gone on to be approved for asthma, eoe, and nasal polyps.
- So this is the initial liberty, asthma trial that looked. This was a phase, 3 trial that looked at patients with uncontrolled asthma. They saw, you can see here on the Y-axis they saw an improvement in Fev. One in patients who received dupilumab, which is different doses, but the blue and lighter blue lines compared to the placebo group, which is like the red, like tan lines on the bottom.
- This was one of their outcomes that they had seen, and this is just, you know, one of the examples of of using immune modulators for lung diseases which any pulmonologist in the room can speak more to that than me. But you know we see that being more and more used in things like rheumatoid arthritis and sarcoidosis, and etc. So this is another interesting follow up study that they did with tupilumab looking at Copd patients, and they saw an improvement in Fev. One. The interesting thing about this is that they were looking for patients with elevated eosinophils. I wouldn't necessarily say elevated, but because our Max Eosinophils that we look at in epic is 600 or 0 point 6, and they were looking at 0 point 3. So just some inkling of a type, 2 leaning response, and they saw a significant change in Fev. One compared to placebo patients.
- So we then looked into large databases and looked for covid-nineteen patients who were prescribed duplimab.

- So this is Trinetx. This is a multi-country 10 plus country database with covid-nineteen patients, and we found close to a thousand patients who were prescribed to Pilumab and had a covid diagnosis in the system and compared them to controls. And these were propensity score matched for age, sex, and comorbidities. and we saw a significant reduction in mortality for those who had been on Dupilumab through their COVID-19 illness.
- We then looked in N. 3 C. Which is a Us. Based cohort us, based database that we saw this a similar effect, and in this case we looked at, we found, close to, or 220 dupiliumab patients who had tested positive for covid-nineteen within 60 days of their dupilumab prescription. So they had been on Dupilumab for at least 60 days prior to their covid diagnosis, and we one to 5, matched them to controls that were matched on age, sex, n. 3 c. Site. Atopic diseases and race and ethnicity, and we still saw this survival benefit with those on Dupilumab. Compared to those not.
- This is the last study I'll point out with Dupilumab, with retrospective data. But this was collaborators of ours out of Mount Sinai, and these are dermatologists who looked at their atopic dermatitis patients during covid, because they also noticed a protective effect with dupilumab. And so they compared their patients. Covid experience between those who are on dupilumab for their atopic dermatitis compared to other systemic.
- So this is atopic dermatitis patients. So Janase Kinase, inhibitors methotrexate prednisone compared to those who had were on no treatment for their atopic dermatitis. So this severity scoring this is like pre kind of the overall severity scores that we all started using, but they had developed their own severity. Score 0, and one means just like little to no symptoms compared to major, mostly healthcare seeking symptoms. And so they saw a difference in their covid-nineteen outcomes with dupilumab.
- So all of that put together led to this phase to a randomized control trial. And the big goal of this study at the time was to one was to assess safety, safety of using this drug in covid-nineteen, and to take these hypotheses and translate it into humans with covid-nineteen.
- So this was our Ind. That approval that we had gotten for for an alternative use to Dupilumab, that we received in spring of 2021, and this was the trial design. So this was an Rct. Looking at Dupiliumab versus Placebo. In addition to standard of care, we enrolled those hospitalized with Covid-nineteen. They were Pcr. Positive. This was easy to know, because we were testing everyone for Covid, and we still do that are entering the hospital and evidence of moderate to severe covid-nineteen, and that essentially was almost all patients were on oxygen, but requiring hospital admission for their covid-nineteen. The exclusion was those already on mechanical ventilation on the day of enrollment the idea being, it was going to be hard to kind of separate out that Pathophysiology from from those in the moderate to severe range. The primary endpoint was ventilator, free survival. At day, 28. We enrolled during our delta phase here at Uva, which we enrolled very quickly from June until November. Really, everything from September to November and we sequenced all the viruses that of patients enrolled, and it was 97% delta. So those enrolled to the dupilumab side received the dosing scheme as that's there on the bottom. And this is just based on the this is based on asthma and atopic dermatitis. This is just the recommended dosage. There's a loading dose of 600 milligrams on day 0, followed by additional maintenance doses on day 14 and day 28, and that was, if patients were still in the hospital and receiving active medical care which one of the main

takeaways from this initial trial for us was just the longevity of illness that we were seeing in these patients.

- So there was a good amount in each group of patients who actually did end up receiving the day 14 and day 28 dosage, and we followed them out to day 60.
- These were the. This is just part of the table one, but this is looking at vaccination status in the cohort. So the majority in both groups were not vaccinated about 60% and the covid-nineteen therapeutics they received not unlike what you would see now. So almost all of them had received steroids above 80% in both groups received Remdesivir. This was during an Il-six inhibitor shortage, so no one had received Il-six inhibitors but genase Kinase inhibitors were received by both groups, and prior to hospitalization. A couple had received monoclonal antibodies all of which, equal between the 2 groups. And so this was our big. What we were 1st and foremost looking for was was any safety signals, and we didn't see. It's a pretty. The nice thing is we started with a pretty safe drug for those that use dupilumab routinely can attest to this. But really the big side effect from Dupilumab is a painless conjunctivitis which we actually didn't see in our dupilumab group we saw in our placebo group.
- And the second thing is an Eosinophilia. It's a transient Eosinophilia. There's no downstream effects of it. There's no symptoms from it. And this was seen in the initial asthma trials and atopic dermatitis trials. So we did see that in our Dupilumab group, and there were no downstream consequences of that.
- So we did not reach our primary endpoint, which was ventilator-free survival at day 28. There was no difference between the 2 groups at that time. When we started we started to notice, but again getting back to that what we had noticed. Looking at these patients for the further out, we looked at them. We saw the bigger difference in the treatment groups. So none of this came to significance. But we did start to see, as we looked further out. Towards day 60, we start to see that a lot of patients that were intubated throughout this period were able to come off the ventilator in the Dupiliumab group. But unfortunately, we're not able to in the Placebo group.
- And so, because of this trend we were seeing, we followed these patients out to one year after their hospitalization, and we saw further deaths happen in the Placebo group, a total of 8 deaths in our placebo group compared to 3 deaths in our dupilium group again, not to significance. But it was something that was interesting to us. We brought these patients back to do pulmonary function testing on them and you can see these. These 4 boxes are. These box and whisker plots are looking at the top left, I think, was the most striking. Finding that we had seen for such a small group.
- We had seen a pretty widespread between our placebo and our dupilumab group in percent, predicted Dlco.
- We basically everybody in the Placebo group had an abnormal percent, predicted Dlco. You can also see in the B box. There's the 6 min walk testing. And then C and D is the Fvc. And Fev. 1% predicted.
- And so our primary endpoint for this follow up study was looking at an abnormal 6 min walk test or abnormal Dlco. And that was based on what was the data that was coming out at the time about patients, persistent pulmonary abnormalities in patients post covid-nineteen along with Pre Covid Ards data. Which showed which shows that Dlco is in 6 min walk. Testing is is the more prominent abnormality that you see post illness. And so we saw a significant difference between our placebo and our dupilumab group again, for it's a small. It's a small study warrants further

investigation, but it was an interesting finding, especially to the degree to separation we saw between the 2 groups.

- We also had collected cytokines. We had collected serum for cytokines, chemokines, and growth factors, that same kind of panel that we had sent that we had sent previously. And we're looking for differences. And what was most reduced with dupiliumab, and it was those patients who had normal Dlco. 6 min walk tests at follow-up had a larger reduction in eotaxin, which is a type 2. It's downstream of il-thirteen tnf. Alpha and IP. 10, which are kind of a macrophage function in calling macrophages over. And so this was also seen in this decline was seen in Tupimab group compared to Placebo.
- So this kind of this, this brings us up to where our current plans are
- And kind of gets into long covid without going crazy down the rabbit hole with long covid. Because I think you can have multiple lectures on Long Covid, and a lot of different arguments back and forth. It's a huge gray area in the literature right now, and there's a lot of different hypotheses. But just to point out a couple of a couple of things that we have been thinking about a couple of challenges we've been thinking about with designing a clinical trial in the long, covid sphere.
- So this is the National Academy of Sciences. They did a this is their most recent long covid definition, and a lot of different associations have a lot of different definitions. And I think that's been one of the challenges in comparing clinical trials is that everybody kind of has their own definition of what long Covid is. I think the second challenge is that it just it's so heterogeneous. These populations, so comparing these folks against each other is also very difficult. So you know, a big takeaway for us is really honing in on the patient population that we're looking to have an impact in what is our hypothesis, and what particular patients in long Covid are we looking to help? Right? And so this is the definition that we are going by, and a couple of things about this definition that I will point out so long. Covid. It's an infection associated chronic condition that occurs after Sars-cov-two infection. A couple of things to say. Something's happening after Sars-cov-two infection these days has its own challenge. Right? Everybody's testing at home. How can we determine if that's, in fact true, that they had a prior covid infection. I think you know, there's there's a lot of people, a lot of folks who who do have that at home test. They save it, or take a picture of it for work, or for friends or whatnot. But still it's a challenge, right? We're not. We're not getting a lot of not as many patients are coming in to get tested right.
- And then I think the other thing, too. And a lot of us know this right is, you know, it's a new. It's supposedly a new condition after Covid diagnosis. Well, a lot of our patients. This is their 1st interaction with the healthcare field, so to what extent do they have a pre-existing in our case? Pre-existing lung abnormalities, and is that due? Is that all happening Post Covid? Or was that happening before? And then maybe there is some impact from Covid. But to what extent was it happening before.
- Is another is another consideration for us. And then I'll say, the last thing I'll say on this slide is this idea of defining long covid by symptoms which is subjective, which is what a lot of the major prospective cohort studies are doing or defining what you're looking for objectively, right pfts or imaging. I think those are kind of 2 things that need to be teased out in designing a clinical trial.

- I think so. We don't have a biomarker that defines long covid, which would be nice. Because then you can, you can kind of you can look at these different clinical trials and be able to relate them to one another. Right?
- Oh, sorry! I said. That was the last, and it's not the last. The last thing I'll say is the timeframe. How long the symptoms! What's the cutoff for? How long your symptoms are before you can be diagnosed with long covid that varies from different depending on the different recommendations out there. But I would say 3 months is pretty standard at this point for a while, the Cdc was saying, one month.
- But this is, this is generally what folks are going by as far as the duration. So this is an example. This is a recent publication that was published about a month ago in CID. This is the Recover initiative folks which we'll get to in the next slide, but these are. They are looking at the prevalence of long covid, or in what I was interested in, is the incidence of long Covid after getting a covid infection, and they looked at 3 different databases. One is N. 3 C. Which we talked about in a previous slide, right? It's mostly us based. And it was organized for Covid-nineteen research. The Pcornet had existed. Pre-covid pedsnet is for pediatric patients. And so you can see that when you use their different definitions, each of them have a different definition for long covid. Some of them are more machine-based learning. Some of them have, like symptom scores. You can see the difference in the estimated incidence of long Covid after covid infection.
- They tried to harmonize it to then that 2,004 Nassim definition that I showed in the other slide. And so you can see that in the light pink in the with that light orange number. So like a 10 to 20% incidence after after COVID-19, I think the big takeaway from this is that it's still ongoing. Long. Covid is still happening to people. It's not. There's no evidence that it's declining after Covid. So it's still their point was, it still remains a public health concern.
- This is a busy slide, but this is the most recent. This is the recover cohort, which is a huge multi-site, like 80 sites in the Us. And Puerto Rico, prospective cohort. Looking at long covid patients, they enroll patients who don't have long Covid, who don't have a prior history of Covid-nineteen, which I think might be pretty hard for them to find at this point. But and they enroll patients who don't have that history. And they enroll mostly patients that have a prior exposure to covid-nineteen or infection with covid-nineteen. And through a bunch of they have a symptom scoring algorithm that they've come up with where they assign different scores to different symptoms, and they're able to predict above a score of 11. They predict that you have long covid. So if you look the thing to focus on in this is over here. So these are the ones that don't have a prior covid diagnosis that do have a prior covid diagnosis. But don't meet the long covid definition, and these are the folks that they are defining as having long covid, so you can see all of the different symptoms.
- This is within their long covid cohort they're looking at. They're looking for different subtypes, which is kind of what we had been talking about, as far as you know. Which specific type of long covid patient are we? Are we looking to make an impact in. And so you can see, it's very complicated. And there's everybody patients have overlapping symptoms. What I'm looking at and what we're looking at for our study is so up here, shortness of breath, chronic cough conservatively estimating, like 30% of the long covid folks is what we're looking to to target.
- We talked about this a little bit in the prior slide. But this is more data showing that the most prominent pulmonary function abnormality post Covid. This was a cohort of patients who were hospitalized with Covid-nineteen. This was their pfts after the

fact from 3 to 12 months later, and you saw that everyone improved over time, but these were the most common abnormalities seen. So on the left there is the Dlco percent predicted, and on the right is the distance of the 6 min walk testing and so this this is A study that was done out of University of Alabama.

- That was a cohort of theirs. This was their pulmonary folks. They enrolled patients with persistent pulmonary symptoms, post covid-nineteen for about a month, and they brought them in and did pfts on them. And so this is like we talked about before combining that subjective and objective kind of data together. So what percentage of people with persistent pulmonary symptoms after Covid-nineteen actually have abnormal pfts, and so that I would say about 60% right from that study.
- And briefly, we'll go into kind of the upstream biologic mechanisms that is talked about in the literature of long covid. What we're looking to impact is the post-acute inflammation with our work.
- You know the the best way, and we've seen a lot of this in the media, especially with regards to Uva and folks at Uva working hard on these things we see that preventing acute infection is probably the best way to go in preventing long covid right being able to prophylax, pre-exposure, prophylaxis, post exposure, prophylax, and vaccinate is the best way to go. We know that if we can reduce the Max viral load achieved, we can reduce the risk of long covid. We know that if we can reduce the amount of time somebody has a viral load, we can reduce the risk of long covid as far as viral, persistent. You know the Rct. That looked at Paxlovid and long Covid patients. It didn't necessarily show any difference in the long Covid outcomes when you give patients paxlovid after their diagnosis. So there's still some work to be figured out. I think there's probably some interaction between virus persistence, and whether that's an active virus or an antigenic stimulation that's chronically stimulating the immune system after the fact. But that is just part of a slew of hypotheses as to what is the cause of long covid, and we are specifically look at looking for respiratory, long covid patients. And what is the cause? What is the cause of that. And what how we can impact that.
- So this is data from the woodfolk lab here at Uva, who looked at cytokines, chemokines, growth factors of long Covid patients patients following up at our long Covid clinic here at Uva. And they were kind enough to look into their data and find this data, seeing these are all type 2 immune markers that are persisting over one to 2 years after infection. There's no control in this, but this is just all the long covid patients that they're seeing in their clinic.
- They also had separated out those patients who had what they were calling abnormal pfts defined as abnormal Dlco and 6 min walk tests again. The reasons behind that is that that's what we're seeing Post Covid. And they did an immune network analysis on these patients, and it's a mixed bag.
- But there are a lot of type, 2 markers in there. The idea. And I think the takeaway from this is that it's not one. It's not one Cytokine. It's likely a dysregulation of multiple cytokines. But how do we get those cytokines back on track towards healing rather than promoting fibrosis and
- And so this is one last study out of this is that same group up in Yale. And they looked at their long Covid patients, Pbmcs and their long covid patients, and they see a lot of signs of T cell exhaustion, and they see a lot of signs of macrophage recruitments that Tnf. Alpha we were talking about. IP. 10, but this is their T cell. Their exhausted T cells are double positive for il 4 and il. 6, and they propose that

this is potentially due to a type 2. Immune overstimulation over a long period of time.

- So the hypothesis that we are coming into designing this. Our next step in our next phase of our study is treatment of those with persistent respiratory symptoms with Covid-nineteen with dupiliumab will prevent respiratory long covid specifically leading to an improved pulmonary function through pathologic type 2. Immune through inhibition of pathologic type, 2 immune responses. And this is just a summary of all the data we had talked about in prior slides. You know. I think we started this more of looking at acute covid-nineteen, and seeing that there's more of a downstream, long-term impact of type 2 immune blockade.
- And this has led to our phase 2 B study design, which we are in the process of, we are submitting UO, 1 applications we actually just heard back on our u 0, 1 application, we scored well, not in funding range. We got a 23rd percentile. So we're getting there. But this trial is designed. So this is going to be a single center. This is just going to be Uva and a decentralized Rct. Design which I'm excited about. It's something new for me and the concept of that being, particularly in our patient population at Uva we have patients who come from very far away, add in the fact that they have long covid. They're not going to want to come to Uva over and over again. So if we can have a mobile health team that goes to them and meets them at their house and collects data at their house. We're going to be more likely to get them to want to participate in this in this study.
- So the the idea behind the study is, we will enroll those with persistent respiratory symptoms, at least one for for a month after their covid diagnosis. So they have to have had the persistent symptoms. After a month.
- We aren't requiring proof of a test of a covid test, but if they have proof of it, it's it's we are encouraging it, but not not requiring it.
- And the patients have to be in that 2 to 12 week timeframe post-covid. So they're not exactly to that long covid diagnosis. But this is a way to enrich our population for those most likely to go on to the respiratory long covid and then, when they meet that initial that initial criteria after recruitment we send a mobile health team to their house to complete a 6 min walk test. If that's abnormal, then they're enrolled. And
- when they and then the randomized one-to-one to receive dupilumab or placebo so do we have these patients at Uva is another big question that a lot of folks in our in our data science area Uva has helped us with and looking at Emr data. But this is our. This was last. So this was this past July was when we last looked at this data. But this is the number of patients presenting with long covid with primary pulmonary symptoms, and I think you get a surge after the winter months, which is in keeping with the national data that we're seeing. But these were. These are the about the numbers, and these are just raw numbers on the on the left. So depending on the time of year, you know, 10 to 15 new patients a month. And this is looking at. There's a there's a specific you u, 0 9 u 0 1 long covid diagnosis. But then there's a pulmonary subset of that in epic.
- This is the participant timeline that we're planning. So patients have to come in on day 0 and at 6 months, and that's, you know, kind of for safety purposes, right where we're giving them an experimental drug. The study drug duration is a lot longer than the initial trial. Again we were more in the acute phase. We were looking more in the hospitalization side of things. This is more of a chronic condition. So we and we like the idea of going more towards the drug dosing that

was originally studied in the asthma and the atopic dermatitis trials and labs and pfts and questionnaires will be done on day 0, 61, 2180. We'll follow them out to 6 months, and in the house at day, 16 day 20. We actually are looking. We have mobile pulmonary function testing that, that we are collaborating with our pulmonary folks, and they are kindly answering all my dumb questions about what to look for, to validate mobile pulmonary function testing so the primary endpoint, I don't think I pointed that out on this other slide. So the primary outcome is longitudinal measures of percent predicted. Dlco and 6 min walk test distance through 6 months. Post enrollment and this is kind of the the assumption for that is that basically that in the group that we'll be able to not only improve pulmonary function magnitude compared to placebo, but perhaps do it faster. Which is why I like the longitudinal assessments. I like the idea of being able to compare our patients to themselves, because I think that's another thing that's lacking, as far as what was your pre existing pulmonary function prior to getting your Covid illness. We don't know that for a lot of people. So this is a way to add a little bit more confidence into into our data. And so our our total N. Predicted end is 170 adjusting for for dropout.

- This is our overall study, timeline. So this is our planned enrollment. This is including all of that data I showed you from Uva, also, in keeping with the data that I showed you about the amount of folks presenting with persistent shortness of breath the amount of folks presenting with persistent shortness of breath and pulmonary function abnormalities. And this is our timeline. We'll enroll over 3 and a half years and the UO. 1 provides funding for a 5 year. A 5 year duration.
- So here's the trial summary, like we had talked about. And I think that's all I got. This is this is just to point out that this is just like this is just the main titles of the groups of people that it takes to. For all of this, all of these people are just completely they they do. They function in in helping move this trial forward, and none of this can be done without and without any of the pieces. So
- Genuinely thank you to everybody. This is like the list that I could. I'm sure I'm missing somebody on this list. But genuinely thank you. This has been. This is quite an exciting body of work to to get to work with. So yeah, any questions.
- Thank you so much for that. And just thank you for the work you do, because I feel like just listening to all that. This seems like a very challenging thing to study. I'm going to ask my personal question, and I'll get some questions in the chat you mentioned about how just the definition of long covid in and of itself, you know, is problematic. Just with all the variability and how we define it. I was curious your thoughts because you mentioned how even the you know, defining what is after Covid right? Really mean and I've was thinking about my personal experience with Covid. I had it, I know, at least twice, and so is there any distinction in the literature around like folks that were reinfected with Covid. How many times, and does that matter? You know, clinically, in terms of how we think about outcomes, you know a person who maybe had the initial infection and then never got it again versus you know, folks that had a later variant of Covid infected. If you could maybe speak to that. Yeah, yeah. Great questions. All great questions. One is to the workload. It's fun work, though, so just it is very fun. And it's very fun to really look at how to answer a really look at how to answer a clinical question and be able to answer it.
- Well, is a is fun. 2. To your question about your question about reinfection. So there is some literature that reinfection. This was a Va. Study, that reinfection with covid-nineteen increases your chances of long covid. I think that's more of a gray area risk factor. Some of the other ones, like severity of disease. Female sex have been

just like proven over and over again in the literature, in the retrospective studies. But reinfection has been shown to increase your risk of long covid. So that would certainly be something that we look at in these patients in collecting their initial data on day 0.

- To your question, what was your last your question about remind me, yeah. So I think just about if it
- I think you kind of answered it. There just really related to outcomes with particular, I guess, like these study drugs. Or if there's any difference in outcomes like it, like is the drug more effective in groups that only had it once as opposed to you know, folks that maybe had reinfection. Yeah. And that gets to another thing that that brought up for me was we do know that there's less incidence of long covid with the newer variants, and whether that's from just a everybody having this baseline immunity probably is a little bit feeding into that. For this study we are planning on collecting viral studies. So nasopharyngeal swabs are out in addition to plasma and protein levels which are viral part of the nucleocapsid of Sars-cov-two, and also serologies which I think well, we could get into. How you interpret those serologies, because you know, in the, in the general population. The seroprevalence is probably pretty high at this point, but it's something certainly to consider all of those things that you had mentioned, and will be an impact in how we look at these patients.
- Yeah, thank you. So question in the chat from Jonathan Truitt, yeah. Do you think Ct imaging would be of value longitudinally?
- Yeah, that's a great question. And that's something that we've talked a lot about.
- And it's sort of it's a it's a so we want to made it. We wanted to make this trial mobile and making it mobile, adding, in Cts is a little bit harder. I'll say that we looked at Cts in our initial follow up study. We did do Cts on patients, and we scored them and looked at differences in scoring between between those who received a pillium and those who did not, and we didn't see a difference. It would be nice to be able to include Cts, we've tossed around the idea of, oh, could we have patients, you know, go to their local imaging center and get and get a Ct along the way. It is certainly something we are interested in. It's not currently planned for for this trial, though and then we have Bill Petrie. Can you say a word about the master's in clinical research, and how this impacted your work.
- Well, thank you, Bill. So yeah. So I was. I was. I did the masters of clinical research, my 1st year of fellowship. And that was when kind of in the beginning of this work, and it impacted the work a lot. I think I learned how to do how to do programming in Sas and R. And I learned about statistics. And I learned about how to design a good study to answer the question you want to answer, and I was directly applying it to analyzing this data in real time. Obviously with a Biostatistician. Jenny, Ma. Is is a mentor of mine and has helped me through it all. But but yeah, it's it had greatly impacted all of this work.
- Yeah. I'm I liked your presentation, and so on. The question I have, you know, with your animal studies, you gave the the anti Thel 13 right at the beginning of the infection right? And then also with the patient studies as soon as they ended in the icu you gave that. Yeah. So are you indicating that what happens chronically is an extension of what happens in the beginning, because I'm just wondering whether there might be different pathogenesis in the beginning and because they have a kind of a cytokine. Yeah, you know, storm like stuff. And later, you know, about 3 or 4 weeks later, could be a different pathogenesis. So I was just wondering before

you embark on this big study. Yeah whether you should take the animal model and then the subset that is chronically affected.

- Give them the il. 13, and see whether it works because it, the Il. 13, may not be operative, you know, may not be involved in the pathogenesis at that point. Yeah you know what this is. A big study you're embarking on. No, you bring a lot of really good points and a lot of discussion has been around this around the timing of dupilumab and I think there. So from a clinical trial standpoint, I think it becomes. There's enrichment for the study population that you want to study right, that you want to enroll in your trial. And we talked about you know how how difficult that is, in the long covid field. But I think there's also like in a perfect world, we'd be able to id these patients when they hit the door. They've got some marker that we're like. Oh, they will respond to Dupilumab, and we can keep them on Dupilumab, for you know, one to 2 months or whatnot in an ideal world. But I think when you're initially starting to study it, it becomes difficult to do that right right off the bat. I think.
- I think, because I think you'll catch in those in those scenarios when you're when you're looking at outpatients, everyone getting covid, everyone doing doopy.
- It starts to. There's a small subset of those that go on to have long covid a small subset of those who go on to have pulmonary long Covid. If we could predict who's going to go on to develop pulmonary long Covid? That would be the ultimate right to be able to know that.
- But I think in the mouse. So in the mouse model, the challenge is to develop a a long Covid Mouse model. I think that that's been, and it's still ongoing in the future. Lab. This being able to have a long mouse that are that live through Covid and are able to to, we're able to study the long term consequences of it is something that is is being developed concurrently with all of this. So yeah, your point is completely. Yeah, it's something that we have.
- We have considered. And we are changing from our initial study. We're changing when we're giving dupilumab. And so a lot of the data out there, you know, suggests that it is the same inflammatory process that's ongoing acutely. That just continues.
- But you're right in that. It's a it's a it's a whole different when you talk about acutely versus chronic, that it's a whole different kind of clinical mindset, and I'm wondering whether but get more out of this week.
- It's big. Yeah, turning, I'm just wondering whether innate cells have a role. Oh, yeah, and whether you can you can inhibit those in itself by putting in some little bit of Prednique, I mean some steroids. Yeah. And then adding, Your
- Yeah, no, that's that's that's very. It's a. It's a very good point, and we we will enroll patients who had been like you can have been hospitalized in that month for your covid illness as long as you're outpatient. By the time we enroll, so, presumably because severe covid, it predicts long covid. Presumably some of the patients we enroll will be those that are hospitalized and those that are hospitalized if they're requiring oxygen are going to get steroids. But yeah, no, it's definitely a a good point. But I really, what we're what we're trying to do is is really narrow down in on the patient population, 1st to test the theory, then to do it on a on a whole population, because I think it would be very. It would take a lot of patients enrolling a lot of patients. But yeah, it's all very good points.
- Patrick. I also have a timing question. One of the things that was really striking to me about covid-nineteen therapies is how sensitive the benefit is to the timing of when you give it so, like Remdesivir, give it early, provides benefit if you give it late.

Some people would even argue the signal for harm. Steroids kind of the reverse. If you give it late, there's clear benefit. If you get early, there's possibly a mortalit harm there. How do you? But in the dupilimate data, if in your prospective trial you gave it hypoxic patients right? And in your retrospective data, presumably these are patients who are on dupilumab at the time of infection, and in both groups saw benefits. So how do you kind of think about that from an immunological standpoint? Is it. Just that. Yeah, Il-thirteen blockade is such precisely targeted for benefit here or something else going on.

- Yeah, that's a good. No, it's that's a very good point, and I think I think it's a it's a part of a of a whole picture. I think there's an abnormal, immune response that happens as a result of Covid. I think you it's that phase of after viral infection, of just being able to blunt the type 2 immune response. And whether or not you were on Dupiliumab prior to, or whenever you get it, you're able to blunting the type. 2 immune pathway is leading to a beneficial outcome. And so the timing of it, I would say, is just that, you know you're not really being on Dupilumab as like a prophylactic to covid-nineteen. Wouldn't really, you know the benefit of it. To doing that is, you know, is not not totally there, right? Because you don't know if you're going to get Covid. You don't know how severe you're going to get Covid, but but but whether or not you're given it acutely versus later on in the chronic illness. I think ideally, you would be giving it acutely to prevent downstream. I do but I think again designing a clinical trial to give Dupilumab to. Everyone starts to get real big numbers. And Patrick, you know, you've been in the Budget meetings so that's the other, you know, big elephant in the room is, how many patients can you enroll with funds? And how can you really get at the question? But yes, in a perfect world. I think I would give it acutely and be able to predict and separate out and have, like a biomarker that's going to determine who's going to go on to have this, this, this phenotype immunophenotype? Yeah did that answer your question? Okay, okay, I was talking. Yeah.
- Thank you. Guys, thank you.