- We try to make certain that our patients don't know any or else your members, and yet there is still 30% that say they have up to
- and it's it's fascinating when I will look through the Pmr. In our system, and i'll see so. And so it's been to the emergency room in the last 3 years.
- and then this start. Summary says
- In the last 2 years this person does not have mild, persistent. They, they may not even have it. But to Co. Code them as well for just an ask on this kind Correct I think there's clear confusion between what is as the severity and what is asked with control. And then you know, how can we start?
- So in 2013 the year I sent me a Yes, I got together and and proposed a definition for severe asthma, and by that definition is as well with capital. All caps for asthma we can acquire
- to prevent it from coming under control, or which remains uncontrolled despite that
- and certainly when you think of that definition, that's an umbrella definite of different things, because it's a very clinically based definition. And if you think of many of our rooms that we grow around in our in our world.
- Asthma is a very similar term to things like cov signicitis arthritis, because the current failure, which are all just general clinical.
- So the 2,003 guidelines suggested that they would be a 3 stage of phone
- to identify the physical as Mo, and then determining whether it was, in fact, severe asthma.
- and the 3 steps included, becoming an admin diagnosis and identifying the patient as having a good call to treat as
- To then number 2 differentiate severe as well from milder forms of asthma. Will these patients improve it? Some practical approaches like that?
- And then, finally.
- so the first step, at least from my.
- and and oftentimes one will see that there's never been an objective diagnosis of it's been labeled as well. They've been labeled as much to, you know, 2,000, and there's never been.
- Asthma is reversible. Airflow, elimination
- and reversible airflow. Limitation.
- Okay, requires that there is an improvement with a bronco, dilator, and oral steroids, and there may be some other nuances of that, but that there is reversibility of 12 in their Fev. One the amount of error that they can get out in the forced exhalation in 1 s
- that has to achieve 200 ml's as well to make a diagnosis of of asthma. And there's an awful lot of people in this space who are called asthma, who never make that that reversibility criteria, and may, in fact, not even have airway obstruction.
- so it requires evidence for reversibility and or hyper responsiveness, and the exclusion of other primary diagnosis, including the presence of irreversible airway obstruction. I think there is a tendency. Well, if someone didn't smoke and they're having shortness of breath, they must have asthma. Well, they still need to have that reversibility component.
- They don't have to return to normal to still be asthma. That's the other sort of extreme is that you'll have people that have a fairly substantial airflow limitation. That and they end up being called Co. Pd. They still reverse. They reverse like they have asthma, but they're called crpd.
- and in the absence of a 15 pack, your history of of smoking, or, more really difficult, severe asthma is much more likely to be the diagnosis, and not

- if you actually do surveys of again general populations of asthma, and you actually hone in on. Do the patients have asthma? 30 of the patients will not have asthma when you apply strict diagnostic criteria.
- and so one of the things that we like to suggest in the guidelines do as well is that when you see a patient with this difficult airway disease, that they should probably be evaluated by an asthma specialist for about 3 or 4 months before you actually make the diagnosis of severe asthma.
- So the second element is to differentiate severe asthma from milder asthma that will respond to various other non asthma medications. So again, as I said earlier, severe asthma is asthma, which requires the treatment with these high doses of medications.
- and patients must be appropriately treated to meet that definition. So how do we move? A difficult to control, patient
- to easier control and thereby not necessarily severe asthma. So we want to address reversible associated factors, things like gastroophageal reflux disease. It's certainly the easiest to address and cure. Now it's probably not driving the asthma, although there's still probably some controversy there, but it certainly can increase your symptoms of cough, which are often correlated with as well, whether they're being driven by the asthma or not.
- Obviously people are smoking. That's something to address persistent allergen exposure, anxiety, chronic rhino, sinusoid is often seen in association with more difficult and severe asthma, but pretty difficult to treat actually.
- and then obesity, which, of course, has been increasing throughout the the Western world for the for the last 30 to 40 years.
- and then you need obviously need to confirm and reconfirm the appropriate use of asthma medications at each of the visits so always address medication use and and adherence that's again has to be top of the list.
- But I think it's also remember important to remember. The difficult asthma has long been labeled as a disease of for compliance, and sometimes it is. But it's really important to go through the list of reasons why someone may not be able to be compliant with their medications.
- I don't like taking inhaled medications. Believe it or not. in young people this sort of being tied to a medication, that this is a crutch. There are many, many patients that don't like to to do that, and then you have to do an inhaler, and you're get this is a very public sort of thing. It's it's very difficult for some people to deal with.
- The medications can be very expensive up until the last few years any combined controller medication of a long-acting bay agonist and an inhale cord to steroid was going to be around $400 150.
- Fortunately we've gotten a little bit better. And now there's things like Good Rx. Where you can. You can actually get some of the lower cost generics for under a $100, but it took us an awful long time to get there.
- and then just people forget, you know life happens, and it's often really difficult to remember to take a pill twice a day. I've been in that situation taking a pill twice a day, and now you're supposed to take an inhaled medication. Anyway, it can be difficult. You just forget.

- and then in patients with severe asthma. Often the medications don't work, and I think that's a big issue, too. People and I taken this medicine every day, and it's not working. I I don't feel compelled to take it. I still have a lot of symptoms.
- and then, of course, they're taking their inhale medications. But we've got about. I don't know 6 or 7 different devices on all of the inhalers that we use to treat asthma. They're all a little bit different, and they all have to be activated a little bit differently, and they all have a slightly different inhalation pattern, and some you use a space for within some you don't use a space, or it it gets very complicated.
- So the good news is that smart help is on the way.
- and I think this is a really important point to make that mild to even some moderate asthma can be treated with. Prn combination, therapy, and prn implies symptom-driven reusable reliever medication as is currently done with Al bureau
- but not using, albeit at all anymore. So there have been multiple studies that that have compared to this approach to daily therapy and really showed equivalent or even better results. 150
- it's can be done either alone, so only this Prn therapy, or with daily maintenance therapy in the background, which is single maintenance and reliever therapy or smart therapy, and both gina and an apt guidelines the current standards for asthma guidelines really support that
- So I think this is the biggest and most important change to the asthma guidelines that has happened in a long time, and I think it's really important to to mention this. So when I'm talking about this new substitute for Albertol, I'm talking about a combined long acting beta agonist
- and an inhale cortex steroid that can serve both as a controller and a reliever. And right now there's only
- 2 different medications
- that actually meet that criteria the most common one is simba chord, which is you destinide, and for moder all. But there's also a momentum up moment it's own, and for moder all which is doolera and that would fulfill the criteria for the long acting Beta Agnes as well. Now I understand that there's some generics for Simba Court. So, anyway, I think we're starting to see some traction with getting more inhaler options for this this
- this approach.
- and if you look at the Gina guidelines, this is from 2,020. basically what you can tell is that when you're starting out at step, one therapy, the recommended treatment is as needle as needed low dose, inhale cord to steroid and for model. So, anyway, either the doolera or the cybercord, or the generics with the alternatives being low dose, inhale cord and steroids. You get to step 2
- daily low dose, inhale cording steroid, and or as needed dose of inhale for steroid and and for moderate. And again, this is the preferred treatment
- for phase, one step, one and step 2 of asthma Care and then, when you get to step 3. Now we're sort of talking about the persistent use of medications on an everyday basis as a once or twice a day combination therapy.
- But I think it's really important to note that the as needed low dose inhale according to steroid for model combination is the preferred reliever across all of these all of these steps of asthma

care, and that's something that's been very difficult for us to implement in the United States because of the cost of inhalers.

- and the fact that most insurance will still not cover an inhaled common, an inhaled combination therapy at 2 inhalers per month. They'll provide one a month.
- but they won't provide to a month. And so if you're going to get to the higher doses, the step 3 and step 4 is where you're using the maintenance therapy twice a day, and then the combination therapy as a reliever. You won't get you? You don't have enough puffs in a single inhaler to actually be able to do that.
- I think there's a big move a foot to to work on that and to improve that. But we're not quite there yet.
- So multiple studies support this period dosing of a very specific combination type, and I've already, I think, emphasize that there's really only 2 marketed combinations in the United States that that apply the lab along acting beta agonists for model is not the same
- as the most common lava in the United States, which is cell, meter all and cell meter all or it's Variation is in asthma, and is in Admir and brio, and all the generics that go along with them. So those are not combination therapies that you can utilize in this format
- for model has very specific properties to it, with such that it can be used as both a quick reliever and a long acting beta agonist add, bear cannot.
- And so, when it's used as a Pr. And drug it's a. It improves asthma, exacerbations, improved symptoms. This is from the New England Journal, paper from 2,019, which again was done by an independent body of folks in Australia and and New Zealand, and I think, showing very nicely whether you're on but as and I this was the maintenance. Bid therapy versus the Pr. N combination therapy that your reduction in annual exacerbation rates was at exactly the same, and the actual number of
- your exacerbations was even better when you use prn lava and inhale cord steroid again with the emphasis that it has to be for moder all in that inhaler therapy.

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Okay. So then, the last step of this is to determine whether the severe asthma is controlled or uncontrolled. And those are things that again it's really important to ask. Every time you see a a patient? what about what about their symptoms? Do they meet symptom control by Acq. By act, asthma, control, question or asthma control test

- or not? Well controlled by various guidelines? Do they have frequent exacerbation. Severe exacerbations are they having 2 or more bursts of of systemic court of steroids in the previous year? Have they had a serious exacerbation? Have they been hospitalized? That takes it to a whole nother level as well
- mit ctl. And is there evidence for airflow limitation? Again, that objective measurement of airway obstruction should be less than 80% of predicted in the presence of a reduced Fev. One to Fec ratio, Evidence of obstruction following a medication withhold, and any one of those 2.
- 4 different categories moves the patient into an uncontrolled category.

- So
- obviously this is just sort of a background of what a patient with difficult and or severe asthma might look like. So how do we actually then
- activate this in the in the clinic? Well, again, we want to identify this patient with difficult asthma. We want to address adherence. Comorbidities risk factors. All of those things need to be done simultaneously, but then it's really important to prove whether they have asthma or not.
- and so the first thing that I do is always going to get a pulmonary function testing on these on these patients.
- and I tend to sort of categorize them as those who have evidence for airway obstruction on the basis of their fee. One or not
- do they have a low age adjusted ratio of fee, one to Fec, and then is their current or present reversibility that 12% improvement in fee, one present. and if you've addressed all those things, there is reversibility present. then they they're very likely to have severe as month.
- That's not what you're going to see often. Unfortunately, often you're going to find that. Yeah, there you go on is less than 80%, and I can't get reversibility
- or their fee. One is pretty normal, and they don't have reversibility. And so the things that I like to do in those cases is actually repeat the spirometry re repeated spirometry with symptoms or with changes over the year, can be very, very helpful. so I tend to get a spirometry testing during symptoms or with a B with a decrease in their background. Medications.
- and you can either show that they're going to be not reversible or obstructed.
- or that, in fact, they are reversible in those cases when they demonstrate that reversibility. You've got severe asthma. And again, it's also important to to comb that emr for previous spirometry testing, because you might find it there.
- So now we've got our patient who has severe asthma now we're going to in 2,023. This is the first time I've given this talk in 2,023. So I had to update the date. We need to bring in the concept of molecular phenotyping and so I think for many years now we've been looking at
- patients as as more than just the the definition of asthma. I reversible airflow limitation in the presence of symptoms.
- and we're really identifying the clinical and molecular characteristics. And certainly the first pass on this was really primarily clinical characteristic so non-specific things like obesity, exacerbation, prone fixed airway obstruction is an affiliate etc. None of these alone really give insight into the underlying causes.
- and then over the last
- tend to now getting close to 15 years. I think we've started to add in multiple molecular measures. So, Genes Mrna, protein expression have been now addressed, but without context. They're also not very helpful. So really molecular phenotyping requires the integration
- of multiple related, clinical, hereditary and molecular characteristics to identify the identify a phenotype and merging of both these clinical and molecular characteristics, then defines a molecular phenotype. And that's where I think we are 150
- mit ctl, and for for most cases of severe asthma today, I don't think we're actually at an end of type level, except in very few cases one.

- And the nice thing about asthma now is that we have these wonderful molecular tools, so we can look at responses to therapy as part of this characterization of these patients, and all of these characterizations are enhanced
- our ability to identify the responses to targeted therapy. So in the last
- 10 years. I think we've really moved to this concept that there's a group of asthma patients I would suggest. It's a majority. It depends on who you ask, but I would suggest a majority where there is evidence of type, 2 inflammation and type. 2 inflammation is really. I I identified now on the basis of biomarkers. And when we're talking about type, 2 inflammation
- in general, we're talking about inflammation. That's related to to 3 different cytokines aisle for an il 13 and or aisle 5 and those cytokines drive
- potentially several different biomarkers. But the most important that we use in the clinic are exhale nitric oxide which is generated from the airway. Epithelial expression of a an enzyme called inducible nitric oxide synthase
- that can be measured in breath as exhaled nitric oxide that's primarily driven by aisle for an Il 13, and it's effect on the airway epithelium or I L. 5, which is very tightly related to Esn Ofills, and yes, and it fills primarily in the blood.
- The relationship would be a in the tissue and the lungs. is actually a little bit less clear. But certainly there's a very strong relationship of aisle 5 and es and fills in the blood. So why are these good biomarkers? Well, as in a fills in the blood 150
- can predict responses to corticosteroid treatment and exacerbation risk.
- this was actually a very lovely study that was done years ago by the asthma, one of the asthma clinical networks that that the Nih, where they actually just had people who were on inhaled cordic steroids and they identified who were not on inhale cord to steroids, and they identified their their improvement in court in response
- to Cortico steroids, whether they had a sine ofills persistently in their sputum, where they occasionally had yes, and fills in their speed speed them, or where they never had esfs in their speed them.
- and what they showed very nicely was, if you had persistent Yes, and it fills in your sputum, and you took inhale cord to steroids. There was a nice improvement in your Fev one. On the other hand, if you had less or no yes, in a bills in your.
- So basically you didn't get a response to inhaled corticosteroids. and if you then gave everyone a broncos dilator, they all got better with a rock and dilator. So they clearly met the criteria for asthma, but only those patients, with esenophiles actually had a response to inhaled according to steroids 250,
- and then, of course, we know from a variety of of different studies. This is from the large Uk database that your risk for an asthma. Exacerbation increases with the increasing number of voicemails in your blood. It's something that I spend an awful lot of time looking at in my clinic population
- as your as as your as an affiliate increase, you get a fairly nice dramatic increase in your risk for asthma exacerbation. So again, something to pay attention to something that everyone can measure 100
- in a basic Cbc it doesn't take a high-powered instrument to actually measure that
- the other by the other biomarker is fraction exhaled in o or pheno exhaled. Nitric oxide

- exhale nitric oxide is in is generated by an enzyme called inducible nitric oxide, synthase which is present in epithelial cells. and in cell cultures. If you treat those epithelial cells with aisle for aisle 13, you will get an increase in in inducible nitric oxide, synthase
- mit ctl, and you can see high levels of exhale nitric oxide across a wide range of asthma severity really from people with allergic rhinitis alone all the way to the most severe asthma patients, 150
- mit ctl, and but interestingly, if you measure high, exhale nitric oxide in a severe asthma population. It seems to predict a high likelihood of systemic cordic steroid-dependent disease 250.
- and it importantly seems to predict the response to aisle. 4 receptor antibody targeted therapy, and the degree of decline in the exhaled nitric oxide actually predicts improvement in F and B one. So this was from the original paper that looked at du Pillumab in in people. and with this is the measurement of excel nitric oxide. Here's the starting point for the group that was treated with Placebo and the group that was treated with theupillium.
- And I think you can see that there's about a 40% reduction in in exhale nitric oxide in the group that was treated with dupilumab that was maintained, even though they were tapering off all of the background medication, that reduction in exhale nitric oxide was maintained, whereas in the Placebo group it rose as you were taking the background medication away. And so again, I think this is important because it is both a predictive biomarker. It identifies people with type, 2 inflammation
- and a response by a marker, so that the greater the decrease in the excel nitric oxide, the greater the improvement in the fee one, and the correlation of that actually was pretty good by human standards. So a negative point for point 4, one in that initial study.
- Now
- we've got these 2 type, 2 biomarkers. how do we use them? So now I think it's really important when you see an asthma patient with severe asthma or difficult asthma, Probably not so important in the mildest of patients. But I think even in that area you can start to think about it now. So we've got our asthma umbrella. We've got all these patients with symptoms, exacerbations, low lung function, etc. Now we want to break them out into whether they have evidence of type, iii inflammation, or they don't
- mit ctl. And we have evidence of type twoi inflammation and to define type, 2 inflammation. It's reproducible biomarkers which predict responses to treatment and that includes right now eccentophyls and exhale nitric oxide, 150.
- The only way that we identify type. 2 low asthma is the repeated absence of those type 2 biomarkers. There is no other biomarkers that we use to identify that group of of patients.
- But I think it's now in 2,023, and maybe even a few years before. Important to say that not all type 2 high asthma is the same
- that there are multiple different sub types of type, 2 high asthma, probably the same for type, 2 low asthma as well. But I think we would all probably agree that allergic early on that asthma. What we were taught in the textbooks is probably the most prominent type, 2 high version of asthma.
- And this was data from the severe asthma research program that I've been.

- It's fortunate enough to be part of now for over 20 years. but these were patients who had undergone bronchoscopy 350 patients had a whole boatload of information collected from them. and that that information was clustered, using statistical approaches
- to break out different phenotypes of asthma, but primarily looking at clinical and some inflammatory clusters characteristics. And I think what you can see is that if we look at the at age that people got their asthma. There were yeah, Most of the patients got their disease
- in early childhood. both what clusters? 2, 3, and 4 and 6 got their asthma in early childhood cluster. One is basically healthy controls.
- what we also then we're able to show is that the relationship to skin reactivity. So allergen prick testing was much higher the earlier you got your disease as compared to getting your disease later in life.
- and so is the relationship to symptoms. When you're around something you're allergic to. so the easiest one to check on is actually furry animals, because people are pretty know pretty much whether they're allergic to cats or dogs. and I think you can see that the Blue Bars means Yes.
- the blue bars are much higher in these free early onset groups over here as compared to both clusters 5. And then this, this very severe late onset cluster and there was a relationship to elevated excel nitric oxide. But, interestingly, clusters, 2, 3, and 4. These most allergic, symptomatically allergic most allergic from the standpoint of skin testing was actually associated with more with milder disease.
- and they had modest type, 2 high type, 2 biomarker inflammation not really profound elevations. But they did have the strongest family history.
- So that was kind of that initial sort of clinical flash, inflammatory clustering.
- I we have been doing now epithelial by markers in bronchoscopic studies now for over 10 years. this was the first of the papers that we published back in 2,014, but I think it still bears a lot of relevance today.
- So we had done micro-rays. This was in the old days before Rna sequencing, and looked at Gene expression and looked at the relationship of gene expression in the epithelium in relationship to exhale nitric oxide. So we took all the genes that correlated with this type 2 biomarker exhale nitric oxide.
- And then we clustered these 500 or so genes and got very distinct clinical clusters of of patients. This basically looks like a checkerboard, which I think probably even people in the back of the room can see
- that the yellow is high. The purple is low gene expression that there's a huge difference between cluster one and cluster 2 and gene expression. There cluster. 2 has really high expression of these things cluster. One has low expression of these genes, and then you have kind of these mixed bags over here in clusters, 3, 4, and 5. But then, if you looked at the gene expression that went along with, or the clinical characteristics that went along with these clusters.
- what you find found was, there were actually 2 clusters that had first of all very low, exhale nitric oxide levels, and then 3 that had very high exhale nitr dioxide levels, and yet their gene expression pattern was really strikingly different. Despite the fact that all 3 of these clusters had high excel nitric oxide levels. You can see the genus version pattern is very different. So in

the 2 low exhale nitric oxide clusters this was a healthy group of people. These were mostly healthy

Unknown Speaker

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control, some mild asthma patients. The

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this other low group actually was. About Half of them were moderate to severe asthma. They had the earliest age. At onset they had long duration of disease. they were 100% a topic, including the 4 healthy controls, and they had high B Al bronco lymphocytes.

- But then, if you looked at
- we're getting to click on these. If you then look at the high exhale nitric oxide clusters. so if we start with a high exhale nitric oxide cluster here on the end, this is again probably the classic asthma, a group of patients that we read about in in the textbooks. These were young people early on that disease. Half were African, American, very strong family history, the highest, ig. E.
- But again very different gene pattern from this cluster, to which was a high exhale nitric oxide. Early onset, moderate to severe disease, high as it fills in the blood and the bal and very low lung function, and then
- mit ctl, and it's finally a cluster number 3 high exhaled nitric oxide, same thing, but really very different gene expression pattern majority were later on sets of your patients 250
- neutrophiles. Yes, and those lymphocytes, very complicated inflammatory pattern and nasal polyps and sinus disease. We're really very key biomarkers of that group.
- So I mentioned early on that helpful in identifying these phenotypes is our ability now to integrate biologics, and that we now have 5 different biologics. Let me so actually 6. Now, different biologics for the for the treatment of asthma, and particularly severe as well. Of course. The first of these
- was anti-g, which is been around now for 25, going on 26 years, which is really hard, hard to believe. but this was the initial. The initial studies were done in what are known as allergen challenge models.
- So allergen challenge means. You take a patient who's allergic to find out what they're allergic to you. Give them increasing concentrations. You have them inhale increasing concentrations of an allergen that they're allergic to, and you measure their long function. And in people that are allergic to that inhalation you'll get a decrease in their lung function. They'll get wheezing. They'll get a mini little asthma attack, and that there's an immediate phase that occurs within an hour. That's called the immediate asthmatic response. They then kind of return back to their baseline.

- and then they have a second fall later on, which is called the late asthmatic response. And so Anti Ig was
- first studied in this allergic model of asthma, and it was very clear that Anti ig had a very nice inhibition of the early response and the late response. So it was very good at blocking the symptoms and the long function changes that occurred after exposure to Allergen in a mild group of patients.
- But obviously these biologics have been used to treat patients with severe disease, not mild allergic patients, although there was an initial effort to do that.
- And I think it's been very interesting, as you now move. Looking at Omalismab anti-hyg and more severe asthma patients
- that the ability of omalismab to reduce as my exacerbations in a more severe population is actually pretty small, it's on the range of about 25% reduction in asthma exacerbation. So here's the Placebo group. Here's Theomalismab group. You can see over this year's period of time. It's a pretty small improvement, and total Ig was not predictive of the response to treatment.
- but was, in fact predicted of the response to treatment, and this was done as a post-hoc analysis, unfortunately.
- was defining the patients by, whether they had type, 2 inflammation or not, and if they had type 2 inflammation on the basis of excel nitric oxide, bloody as in the bills. Or this other thing called Perry Austin. there was a very nice ability of anti-e to decrease their exacerbations in that subset of patients which you did not see if those type 2 biomarkers were not increased. So again, helping us to kind of
- focus, maybe not so much on just the Ig. But really on the inflammation that perhaps was driving that now, because the type 2 biomarkers are very tightly linked to type 2 cytokines.
- I think you can suggest that maybe blocking a little bit higher up on the cascade might be worthwhile looking at. And so the aisle for receptor to plyomab was developed. Sorry the aisle for receptor antibody was developed to target the aisle for receptor, and the aisle for receptor is on 2 different subtypes. It has 2 different subtypes of receptors, the type, one receptor, and the type 2 receptor, the type. One receptor, is really present primarily on immune cells.
- The type, 2 receptor is very, very widely distributed. The type, 2 receptor will be activated by both aisle, 4 and aisle 13, the type one by only aisle, 4 and the aisle for that is generated can actually lead to the development of T. H. 2 cells isotype switching of plasma cells to generate. Ig: so really, I think, connecting it to the I gee pathway. And of course, then du Pillomab is this antibody that blocks it
- mit ctl and the in, and we know from earlier studies that inhibition of the aisle for receptor decreases ig. And blocks inhaled an allergen challenge so so pretty similar to what you saw. With blocking Ig. It was able to block those inhale allergen challenges 150,
- but it possibly did it by decreasing the levels of ige that were present.
- Now, how does that translate to to severe asthma? So the the good news is that when you blocked a little bit higher up that the type 2 biomarkers that were used to identify the responders to Omalismab also predicted responses. to treatment with du Pillum. App.
- so again. This is a group of patients with severe asthma on high dose combination therapy for the most part somewhere on the lower dose. Treated with Dupillionab and looking at the effect on asthma exacerbations.

- And I think you could see that if you look at patients with iosenophylls that them if they had no elevation in their ecosystems. They really didn't get an effect as you went up on the levels of eccentophiles in their blood there was an increasing reduction in asthma exacerbations. Similarly, if you looked at, excel nitric oxide again, maybe a tiny little effect in this low group here, but for the most part it's Driven by the presence of these type, 2 biomarkers, and really very substantial reductions in in asthma exacerbation 150

Unknown Speaker

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By the time you get to this

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to the type 2 high, the very type 2 high groups in the range of somewhere between 50 and 65% reductions as opposed to the 25% reduction, or even the when you start to massage the data, the the more 40 to 50% reduction that you get with anti, ig

- mit ctl. And so that's sort of one of the groups that probably the most predominant group of type. 2 hy asthma are those early onset people. But then we also have late onset disease so late onset t 2 high disease, one
- mit ctl and is also seen, and I think this was very clear in our initial clustering that there was a group of patients who got their disease very late in in life as compared to to the rest 2,
- and if you looked at their skin test reactivity, it was much less. If you looked at the presence of nasal polyps. It was very high, and they had the presence of of type 2 inflammation. But again, this is a very low clinical allergy cluster They didn't have response, or they didn't report a lot of clinical symptoms when around furry animals, and this was really vastly different from early onset disease.
- So these patients are well known to have pretty high. Yes, and it fills in in the blood. And so it wasn't too surprising. that would also be a target
- for treatment of severe asthma. and the target that was chosen was a cytokine called an tile 5, which is actually a very important to is in a field development and survival, not so much migration, but development and survival. And when it this anti- il 5 approach was used initially in broad populations of of asthma patients. It didn't work. It also didn't work in an allergen challenge model. So that same allergen challenge model
- that I showed you with ominismab and dupillionab
- didn't, and tile 5 didn't work in that system

- mit ctl. And but targeting patients specifically with the ascent fills it. Did show efficacy. So maple Ismab targeted patients with Yes, and fills greater than 280. There's another one called Resolution, that targeted a little bit higher. Es, and it fills 150,
- and there's always been this consistent 40 to 50% reduction in asthma exacerbations
- in treatment with the Antonio. 5 pathway inhibitors, with some improvements in fev one and asthma control questionnaire results as well. But really the biggest effect has always been on exacerbations. Now I think it's actually very interesting if you start breaking down
- how people, or which people respond best to the anti-ele 5 therapies one there were several striking things that that came out so certainly the most severe patients one.
- If you were on oral cortico steroids, you actually had a reduction in a sorry greater improvement in exacerbations as compared to not being on oral cortico steroids. but one of the in other striking findings was that if you got your disease later in life. If you got your disease after the age of 18, you had a much greater likelihood of responding to an tile 5 than, or auntile 5 receptor antibodies compared to those patients with early
- onset disease, and not surprisingly. And along with this, if you had nasal polyps, you were also more likely to respond. And all of this, I think, suggests that there's a difference in the path of biology of early onset versus late onset. Yes, and aphilic asthma.
- We also know that du pillomab and tile for receptor antibodies also work very well in late onset nasal polyp disease, and that, in fact, if you have nasal polyps, there's probably a greater improvement in your Fev one, and a greater improvement in your asthma call, and in your asthma symptom scores. If you have associated nasal polyp disease.
- It's also approved, for nasal polyps, and again supporting this involvement in the aisle 413 pathway in patients with type, 2 high asthma who have laid on such disease and nasal polyps. And I think these keeping the in mind these comorbidities is actually really important when you start to treat patients with more severe asthma.
- Now, oral cortexteroid dependent patients, these have always been the bane of our existence.
- and I think it's actually interesting. When you look at the clinical characteristics of these people on Oral Portuguese, your eyes are these a different phenotype? Just that they require, or corticisteroids, or are they more of the same? So these were patients in the generalism app study of oral corticosteroids sparing? And I think you can see that these patients had a lot of exacerbations up to 3 exacerbations in the previous year. but interestingly 30 to
- 35 of them had a history of nasal polyp. So again telling us that there's some overlap with these very severe patients and some of these comorbidities things like nasal polyps.
- So all these type 2 biologic seem to reduce or to steroid use in dependent patients. From the standpoint of du Pillumab the generalism app and meppalism app there's data on all 3 of them. this is data on generalismab showing that there's about a 75% reduction in oral cortex Steroids on generalismab is compared to placebo very similar data with dupilium app, so they all seem to have about the same floor of 75% reduction.
- And I think it's. It was interesting that even though the dupiliomab study didn't actually recruit for patients who were on the Ascenophiles, they just said we want oral corticosteroid patients the is in the pills. We're still elevated in these patients with oral corticosteroid dependency, and 30% of them had nasal polyps and late onset disease.
- So

- you were introduced to the concept of asthmatic granulomatosis. Thank you very much. And this is what I call typed
- type 2 plus asthma or autoimmune. Now I’m kind of moving towards auto-inflammatory disease or asthmatic granulomatosis.
- And this is a group of patients who have very severe disease they're all on system and cordic steroids. They're typically laid on Set They often have very high exhale nitric oxide and systemic cord crysteroid use
- it's associated with a strong family and personal autoimmune history. When we do thoricoscopic biopsies on these patients, we actually were able to identify Granulomas in the lungs of about 50% of these patients.
- and I think it's kind of fascinating that there's now multiple studies coming out that are showing a relationship between asthma and rheumatoid arthritis. We've always known that there's a relationship between asthma and inflammatory bowel disease. So there's other processes going on in these patients. I think that make them much more difficult to treat. And this is really the pathology from one of our patients. Here's a a small airway. I think you can see this looks pretty nasty. It's, you know, plugged with mucus. There's a lot of influence
- around it's got goblet cells everywhere. It looks like an asthmatic airway. But then, over here. You see this granuloma, and you see scattered Granuloma's throughout these biopsy. So again, very different from what would one would consider typical asthma pathology. And these are patients who I actually have had success with treating with the type 2 biologic and an alternate immunosuppressive something like an as a thioprin or a methotrexate, in addition to their type
- to for approach.
- So finally it just a couple of words on the non-type too high asthma, which still does exist. Are we making any progress there? I actually think it's unclear. What percentage of patients with true asthma have
- type 2 low asthma? I think it. It is likely that if you do repeated measurements of excel nitric oxide and or bloody as in a field, you'll have at least 60 to 70% who meet criteria for type, 2 high asthma. And obviously where I’m. There on high doses or all Cortico steroids will suppress
- mit Ctl. And they're type 2 biomarkers. So one of the potential cytokines that has been postulated to be important is aisle 6, 1 1.
- It's certainly in data from the severe asthma research program and the Ucsf cohort. There is elevations in aisle 6 in patients with more severe disease, and it seems to associate with
- elements of metabolic syndrome, including a history of hypertension and a history of diabetes, so that you have higher levels of Il 6 in these particular patients. And then, if we look at the relationship of aisle 6 and bloody asenophylls to future exacerbation, risk.
- Interestingly, the relationship of increasing aisle 6 is actually a little bit stronger than the relationship of bloody is, and bills to as of exacerbations looking forward over time
- as compared to the Islamic fields, which again replicate what's been published before. But the aisle 6 story is a little bit stronger and it's very, I think, important to know that there's a now a study on going with anti aisle, 6 in severe asthma. that has been being done by the precise networks. Nhs nhl Bi. Sponsored adaptive clinical trials network where they're targeting aisle 6. and so we hopefully, we'll have some data

- to know whether that really has an effect.
- And then, of course, the newest biologic which has been marketed as a type. 2 low drug is anti tslp
- tslp imoastromic lympho poison is a central innate, epithelial, alarming. it really is probably produced by epithelial cells, probably by macrophages. it seems to interact with a lot of different pathways, including a a lot of different cell types, including Ilc, 2 cells, mass cells, and then can induce the production of of type, 2 cytokine. So again, it's a very complex sort of media

Unknown Speaker

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later

UVA Medicine Grand Rounds

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in some initial studies. when you blocked and block Tslp with the antibody, you were able to reduce airway hyper responsiveness which no other drug actually has shown Yet.

- and it was also like Antonio for receptor antibodies and anti- ig able to reduce responses to inhaled Allergen. and it is the newest, FDA approved biologic.
- interestingly, the only when they looked at biopsies. The only thing that actually got better on the biopsies was a reduction in eosenophyll, so I think it's a little. It's a little early to say whether it is, in fact, a type Iii. Or a Type Iii. Low Drug. And, in fact, when you look at their clinical data, this is from the pivotal phase. 3 study what you see is Yes, indeed, there is a an effect to decrease exacerbations in patients with low-ish blood. Yes, and it fills it.
- and this sort of less than 150 range, but it clearly gets better. there's more of reduction. The the higher the amount of type, 2 inflammation that you have very similar with what was shown with excel nitric oxide. So the more evidence you have for type 2 inflammation, the greater the fx of the drug.
- So just to kind of give you this little summary, then, of how I think about treating the severe asthma patients. So again, here's
- severe asthma. We've already defined it. We're going to divide out the patient into whether they have a type 2 high inflammation or not. and then once we do that, we're going to define them as refractory type, 2 low disease or a factory type, 2 high disease.
- Then we want to look at whether they got their disease early or late in life. I think that's actually really very helpful to divide them out into early versus late onset type, 2 high or type 2 low disease.
- I think, in these patients who you define is type too low. If they're still having difficulties, and you haven't figured them out taper. They're inhaled quarter to steroids. See if you develop

symptoms and see if you've developed a increases in type, 2 biomarkers often you will, in which case you're going to move them over to the type 2 high category of patients.

- and if you've got these type 2 high biomarkers again, you're going to move them over if they don't have those type 2 biomarkers, then you you got a lot of problems. but I start to look for a metabolic issues in those people. These are patients I would consider for Thermoplasty. Certainly, if they're not on a llama, they should be on a llama, and you're going to do all sorts of other autoimmune site types of testing. Do they have another type of process that is driving the disease.
- And all of these patients over here with type 2 high asthma. Now you're going to follow the type 2 high, severe asthma protocols. But if they don't respond now you've got to consider all of these elements as well.
- So, in conclusion, difficult and or severe. Asthma are truly umbrella terms with severe asthma subset of difficult asthma then once identified, I think it's very important that you divide patients with severe asthma into those who need evidence for a active type. 2 inflammation versus those that Don't.
- And then I think precision medicine can and should be applied to treatment of type. 2 high, severe asthma, where we really have made huge progress over the last 10 years, I would say, and have seen substantial improvement in outcomes. So I’m going to stop there. I'm happy to take any questions, and I thank you very much for your attention.
- Pick off the questions. Thank you, Dr. Wesel.
- One thing you know, every time we think about nitric oxide anywhere else in the body. We kind of think of vasodilation.
- So their thoughts that this is a mechanism that is putting severe asthma into like a pulmonary vascular.
- a disease, and not a small or not an airway disease. Well, yeah, exhale nitric oxide is a fascinating biomarker, and and you know yes, nitric oxide can vasodilate it. Can Bronco dilate. And so we're just talking about nitric oxide wouldn't nitrate oxide. Be good, you know, at some level.
- But I think when we're measuring nitric oxide, we're just measuring the tip of the iceberg. And so there's all sorts of oxidated nitrative processes that Jerry Teams been very interested in Ben Gaston when he was here, was very interested in, etc. that can alter the nitric oxide and give you these really toxic sort of potential, and I think, in patients with more severe disease. We're looking at that element because there's clear evidence for oxidative stress pathways being activated
- more severe asthma, and not so much the no broncos Dilator. but in milder patients I actually think it is a broad but dilator, and it is a good thing, and it's probably beneficial.
- Excuse me. thanks, Dr. So my question is about this: t plus phenotype and that there's association with Granny Lomas and biopsy. Is there any association with tertiary lymphoid structures in those biopsies as well? no, not that we've found. Now, again, there's there. We we've occasionally seen Walt.
- but that's that's really rare actually in the in these patients to see that and there's certainly never been any evidence of increased lymphedinopathy anywhere on Ct scans media styled Healer. No. So in a relationship to us AR quite sort of of state.

- so no we really haven't unlike some of the Copd patients, where I think there may be an increase in involved in in their airways.
- Sally, Great talk. Thanks for coming so in certain patients, if one biologic is good, would to be better.
- really good question. Certainly not good for our economic systems if it was better.
- But I you know I really have rarely tried to get to biologics. It's just it. I find, ethically, it's hard to justify, unless somebody is, you know, literally in the hospital 5 times a year I struggle to do that.
- but I think there absolutely could be benefit for having a patience on a dupillionab and an and tile 5 of some sort. because you do get this weird effect on ecosystems with the pillimab, and maybe having them on an anti-fi would actually be a good thing. I just I there's very little data on it.
- Hey? Sally really nice talk.
- So you got me thinking about this stuff which I have not done in
- forever. So my apologies over that but a beautiful presentation in regards to the phenotyping. The second part of that. That was as you started.
- You talked about the change and shift into
- taking a prn approach for many of these patients. And you know my old school education kind of kicked in on the variability of asthma, and I wondered if you had any comment about that, as it relates to
- to the change in the biomarkers, because it dawns on me as you laid out that algorithm
- execution can actually be pretty tough.
- Well, yes, and no You know the good news. These are fairly cheap biomarkers, right? But Cbc. Is about as cheap a biomarker as you can get.
- and I will literally. When I see a new patient I will pull up my epic you know. lab flow sheet and look at the isn't it bills over the last sometimes 15 years that have been in there, and I'll go with the ups and the and the downs, and if over 15 years. There's never been any as an affil there ever.
- I'm pretty comfortable. This is a T too low asthma patient, and even in those patients that I don't have that on.
- I will. If they're a severe patient, I will typically bring them in every 3 months and see them every 3 months, and I I will get a Cbc on them almost every time, and i'll manipulate their inhaled court steroids, etc. So I think repeated measures is really important here to kind of fit them into the right t to higher low block.
- That's actually the key part of my question was really the
- Mit ctl, and understanding that there could be some seasonal variability. The influence on that on those biomarkers and how to apply. Yeah, you know, the whole seasonal variability thing is kind of interesting because 150
- Tom's gonna yell at me. But the the seasonal allergen component here, and then Tom won't yell at me about this, but the seasonal allergen component is actually very minimal, not to say that there can't be indoor allergens that are playing a significant role, but the seasonal component, I think, in the more severe population is actually
- pretty minimal.
- Just to correct one thing.

- what's actually happened with the seasonal thing? Is, it's actually shifted from grass and right
- to the ponds in the spring. So the dominant symptom is actually birch and oak, both in Boston and here.
- and that is primarily due to the increased amount of air conditioning indoors.
- which is probably changed. The dust might signal as well, but I'd like an but there may be a difference in mild asthma. I think.
- Tom, I I do get out later. A couple of years ago we had a we had a little bit of excitement about
- Ph falling in the lungs with John Hunt and Ben Gaston, and you met you raised the name of Ben Gaston.
- Do you think it was ever proved that it was wrong, or was it just that John lost interest in it.
- and went off to Liberia? He went off. It went off to actually solve the whole problem of pediatric
- disease in Liberia, which was a bit of a difficult No, I I I think there were multiple problems. I think Ph. Could still be very relevant. I do. I think it's very difficult to measure and because there's, you know, unless you're preserving that sample appropriately, and keeping it iced, and so on, that the Ph is going to vary because of atmospheric elements.
- And so I don't. I think the answer is, Still, we don't know but I would be very surprised if there isn't a ph element actually.
- there's clearly an oxidative element here. Clearly, the signals are just enormously strong. from the standpoint of worsening disease, worsting oxidative potential in those patients or less oxidative potential, I guess. if you're talking about the anti accidents.
- Thank you.
- Well, thank you, everybody