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Released: 09/12/2025
Valid until: 09/12/2026
Time needed to complete: 60 minutes

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Collaborative Care for CRSwNP Expert and Patient Insights

Announcer:
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Jill Harrison-Snyder:
Welcome to Collaborative Care for CRS with NP: Expert and Patient Insights. My name is Jill Harrison-Snyder, and I'm going to be your host for this program from DKB Med.

We'll kick off by sharing our essential faculty members. First off, Dr. Stella Lee, Chief of Rhinology at Brigham and Women's Hospital and Associate Professor of Medicine at Harvard Medical School. Dr. Katie Buchheit, Assistant Program Director of the Allergy and Immunology Fellowship at Brigham and Women's Hospital and Assistant Professor of Medicine at Harvard Medical School. And finally, Dr. Michael Wechsler, Professor of Medicine at the National Jewish Health and Director at the NJH Cohen Family Asthma Institute.

This educational activity is supported by an independent medical educational grant from Regeneron Pharmaceuticals. All activity content and materials have been developed solely by the planning committee members and faculty presenters.

Dr. Lee:
Thanks, Jill, for that introduction. I'm very excited to start this program. So at this point, I'd like to welcome all the learners joining us for this program. I'd also like to welcome our faculty panelists, and we also have patient panelists with us. So if we can get started with one of our first faculty panelists. Dr. Katie Buchheit, would you mind introducing yourself?

Dr. Buchheit:
Sure. Thank you, Stella. I'm Katie Buchheit. I'm an allergist/immunologist from Brigham and Women's Hospital in Boston. I'm happy to be here today. Thank you.

Dr. Lee:
And Dr. Michael Wechsler.

Dr. Wechsler:
Yeah, thanks so much, Stella. I'm Mike Wechsler. I'm a pulmonologist and a Professor of Medicine and Director of the National Jewish Cohen Family Asthma Institute, National Jewish in Denver, Colorado. Thanks for having me.

Dr. Lee:
Thank you so much. And we have our patient panelist, Carrie.

Patient Carrie:
I'm Carrie, and I'm from Massachusetts.

Dr. Lee:

And Parker?

Patient Parker:
Hi. My name is Parker Happ. I live in Massachusetts I'm a patient of Dr. Buchheit and I'm excited to share my story.

Dr. Lee:
Wonderful. Thank you so much. I'm very excited to start this collaborative care for CRS with NP: Expert and Patient Insights.

These are our disclosures.

And the learning objectives for today. First of all, we want to discuss the pathophysiology and the burden of chronic rhinosinusitis with nasal polyps, or as we'll refer to as CRS with NP. Identify the challenges present in conventional treatment options for CRS with NP, and also discuss some of the newer clinical trial data for some of these monoclonal antibodies that treat CRS with NP.

Let's get started with the burden of CRS with NP. Patients who have nasal polyps, they can fall into many different categories, and there's a huge diversity and heterogeneity in this condition. So CRS with NP is a broad umbrella term, but there's definitely many different subtypes of CRS with NP. As you can see here, we have patients who have aspirin-exacerbated respiratory disease, or we know as AERD. We have patients with allergic fungal rhinosinusitis. And then, as you can see here, there's also other patients who have different conditions, such as cystic fibrosis or immune deficiency, primary ciliary dyskinesia. And there can be probably other subtypes that we haven't even really described or understood just yet.

CRS with NP is a common condition. Over 11 million adults in the US have this condition. And the prevalence of nasal polyps, if you look at all CRS, is about 1/4 of all patients who have nasal polyps, 75% do not have polyps. But there really is a overlap of what we call endotypes, which is understanding the inflammatory mechanisms underlying this condition. So even patients who don't have polyps also have something called type 2 inflammation, and we'll discuss that in more detail.

Age of onset is interesting. This is an adult-onset condition, but there are patients who present younger than 42 years of age, as we see here, which is the mean. But the diagnosis range can be from 40 to 60 years. And once you hear from our patients too, oftentimes, sometimes the diagnosis is delayed by quite a bit of time.

When you look at the symptom burden, patients suffer quite a bit. They have significant problems with breathing through their nose, not being able to smell, having a lot of discharge from their nose, problems in general with interruptions to sleep, anxiety, depression, productivity. All of these things are very, very important. So it's critical that we acknowledge this and ensure that patients are asked about these symptoms, because oftentimes a lot of these can be attributed to other things that might not be actually specific to CRS with NP. And these symptoms can be quite vague as well.

So I'd love to hear from our patients here, Carrie and Parker. So let's start with Parker. Could you tell me, and tell us your perspectives on what your journey has been for you?

Patient Parker:
Thanks, Dr. Lee. I think the biggest part of my story was I felt like I had a cold and it wouldn't go away at the onset. And when I think of the, you know, patient burden and what that meant for me, it meant on the first date I ever had with then my girlfriend, now wife, I was profusely apologizing for essentially being a snotty mess. It was embarrassing. And even being in the office and having to constantly grab new boxes of tissues or sneezing was, you know, a huge burden. As well, I'm a foodie, so not being able to, you know, taste or smell food the way that I remembered—everything basically seemed like it was oatmeal—that was, you know, frustrating. And, you know, just the sleep or disruption in sleep, that just has cascading effects across, you know, quality of life, whether it's, you know, reduced concentration, you know, just not feeling well in the morning or well rested. So just had, you know, issues across the board for, you know, my personal and work life.

My time to diagnosis—I'm one of the lucky ones, possibly because I'm in sales and persistent and pushy, but I knew I didn't feel well and kept asking for more. I was pushed to an allergist and then a pulmonologist, where I, you know, had a spirometry exam that showed I, you know, had asthma, which was weird. And then, you know, we finally went and had an endoscopy down in my nose, and they said, 'Oh, you have a deviated septum,' which might have cleared some space for breathing. But less than 6 months later, I was back, you know, complaining, until finally when I got my first polypectomy and diagnosed with, you know, my condition is AERD. I got on a, you know, path to feeling better and like myself—smelling, breathing, tasting.

So, definitely burdensome, but I feel fortunate that I was one of the lucky ones in my time to diagnosis. So that's a little bit about me.

Dr. Lee:
Carrie, do you mind sharing your perspective?

Patient Carrie:
No, I'd be happy to. I'm one of those people that didn't get diagnosed for a really long time. I didn't even remember what it was like to breathe through your nose. I'd been blocked for years and years. They sent me to allergists, nothing much came up on the panel. I always carried tissues with me. I had a hard time sleeping, and I would wake up and I'd feel tired as soon as I woke up. And I couldn't figure out, you know, why I was tired.

And there was a lot of testing, and I actually got diagnosed by accident. I was feeling hoarse, so they were checking that out, and they were like, 'You have polyps.' And, you know, no one had thought about checking me for polyps all the years of, you know, constant rhinitis. You know, my family, you know, would say—or everyone would say to me, 'Do you have a cold?' And I'd be like, No, this is just normal. I even got to the point where I didn't even know it, and although everyone else was constantly commenting, you know, 'Are you sick?' And I'm like, no, I'm not sick. So it really had a profound effect on my life, particularly with energy level, fatigue, and concentration.

Dr. Lee:
Yes, absolutely. Thank you so much for sharing that. It's so interesting how any of us can become used to feeling a certain way, but that's why this condition is so tricky. But thank you so much for sharing.

I wanted to talk a little bit more about the disease severity with different subtypes of CRS with NP, but specifically also focused on AERD, as Parker mentioned too. If you look at these graphs, you can see that patients who have comorbidities—and this is the whole point of this—is that patients who have comorbid asthma and/or then comorbid AERD, the patients with AERD have the most severe radiographic scores. They're the ones that potentially require more sinus surgeries, as you can see here, and also need more systemic corticosteroids, which we're really trying to avoid. And then you can see the trend as you add comorbidities, that these patients do more poorly. So it's really important to recognize the impact of that.

So I'd like to now invite our co-panelists, Katie and Mike, to give us perspective. Katie, when do you refer and get the otolaryngologist or rhinologist involved when you have a patient who has CRS with NP? And what kinds of things are you looking for or expecting?

Dr. Buchheit:
Yeah, this is a great question. And you know, I think both Parker and Carrie pointed something out, which is that I think a lot of patients who present with nasal congestion get referred to allergists, thinking their symptoms might be due to allergic rhinitis. So, you know, when I see a patient with congestion, I ask them a lot of questions about sense of smell and other symptoms that are consistent with chronic rhinosinusitis. And if I, you know, am suspecting that at least part of their disease is driven by chronic rhinosinusitis, I'm going to get them over to an otolaryngologist early on for good nasal endoscopy and evaluation from that standpoint. So you know, I think that the earlier that we can employ multidisciplinary care, these patients do really well.

And then in terms of referrals, I share a lot of patients with pulmonary as well, you know, managing a lot of the comorbidities associated with chronic rhinosinusitis, including things like bronchiectasis and severe asthma, and EGPA. So really, these patients are quite complex, and it's really helpful to work together as a team.

Dr. Lee:
Great. Mike, your perspective on how to work together, and when do you, and how do you engage your multidisciplinary team?

Dr. Wechsler:
Yeah, well, as you showed in the prior slide, there are many patients with asthma that have comorbid chronic rhinosinusitis and vice versa. I'm seeing them mostly from an asthma perspective. And what we've seen is that the chronic rhinosinusitis makes the asthma worse, and also the asthma makes the chronic rhinosinusitis worse. So it's critical for us to work together as a team, for us to try to identify these patients, to ask—even if I'm seeing them for their asthma, well tell me a little bit about your sense of smell, tell me about your nasal congestion. And then I work in conjunction with the ENT docs, with the allergists to try to address and mitigate many of their symptoms.

Dr. Lee:
Yes, thank you so much. I'm really impressed that you also ask about sense of smell, because that's such an important symptom, and oftentimes completely missed. Even sometimes patients too, they say, 'Oh, I didn't realize my smell has been diminished for so long,' until the smell returns. So thanks, Katie and Mike.

Moving on to management of CRS with NP, you can see that basic diagnosis of CRS with NP, patients have to have symptoms of nasal blockage, smell loss, drainage, facial pressure, pain for at least 3 months. So that also has to be verified with objective findings. So there has to be either a good nasal endoscopy—and in my opinion, every patient with this condition should have and deserves a really good nasal endoscopic exam to get a good view of the lining of the nose because there could be other diseases that mimic polyps. And also

another objective test is a maxillofacial CT scan.

So with the symptoms, as I mentioned, for 3 months or more plus one of the objective findings, that gets you the diagnosis of CRS with NP. Bu there are many different care pathways, as you can see in the EPOS 2020 guidelines, that a lot of patients present first, as we talked about, perhaps to an allergist or even to a primary care doctor, or to a laryngologist. But the first line of treatment, oftentimes when a patient is diagnosed, is saline irrigations, a topical nasal corticosteroid spray, as well as avoidance of things that potentially can be harmful, if we can help it, such as oral corticosteroids. Obviously, they are effective when it's absolutely necessary, especially for asthma exacerbations or severe sinusitis exacerbations, but the mainstay is topical corticosteroids.

The other things here are the presence of alarm symptoms. We worry about, as otolaryngologists, if there's unilateral disease—if there's polyps just on one side, that traditionally is not thought of as this condition of CRS with NP, or could be a tumor of some kind. If there is any orbital symptoms, because the sinuses are so close to the eye and brain, if symptoms related to vision loss or neurologic symptoms, we are also very cautious about that and work that up differently.

Moving on to what we are talking about with just the diffuse bilateral CRS with NP, some of the different options that we have available as we talked about, we definitely categorize between bilateral, which means diffuse, which is all the eight sinuses are typically involved, versus localized or unilateral CRS with NP. And the sinus CT scan is very helpful for that, because we can really understand the involvement, because the polyps sometimes are just the tip of the iceberg.

So going back to our faculty panelists, love to hear your opinion on what is really important for workup for these patients. So Mike, what are your thoughts on things that you do in your office when you have a patient with CRS with NP? Your basic evaluation, we'd love to hear your opinion on that.

Dr. Wechsler:
For me, as a pulmonologist treating these patients primarily for their asthma, I want to get a sense of the severity of their sinusitis and the impact that it's having on their asthma and also, what type of asthma do they have, and what type of CRS do they have.

So I'm going to, first of all, evaluate them with CAT scan of the upper airways. Sometimes I'll do a CAT scan of the lower airways as well. I'm obviously going to do spirometry to evaluate and assess the severity of their asthma, and evaluate their lung function.

And then, in terms of trying to identify what type of asthma they have, what type of CRS they have, I'm going to look at specific biomarkers. I want to evaluate their eosinophils in their blood and/or in their sputum. I'm going to look at exhaled nitric oxide measurements. And I'm going to look at their propensity to allergies by referring for allergy skin testing. Sometimes I might do specific IgEs for allergens, and I'm going to look at total Ig as part of my workup. I also want to make sure that they don't have anything else going on, and so I'm going to do a chest x-ray in just about every patient.

Dr. Lee:
Now, it sounds very comprehensive. I was curious with Katie. There's a lot of overlap there, you know, when you have this kind of team—this is like the dream team here, what do you also do that's maybe different or, you know, complimentary?

Dr. Buchheit:
Yeah. So I think, you know, we kind of think through a lot of the same processes in terms of, you know, certainly workup of any lower respiratory symptoms, comorbidities, and we'll do, you know, spirometry and/or pulmonary function testing, as well as chest imaging, as indicated.

But from the allergy perspective, we'll often, you know, certainly, if there is an environmental allergy component that might be driving symptoms, we will do allergy testing so that we can provide the patient with ideas about how to avoid specific allergens. In some instances, we'll start allergy immunotherapy, if, again, there's really comorbid allergic rhinoconjunctivitis driving a significant proportion of symptoms.

And then, you know, we have at our hospital, an Aspirin Exacerbated Respiratory Disease Center. So we think a lot about, you know, drug allergies, and you know, patients who are sensitive to aspirin and will sometimes do aspirin challenges or NSAID challenges when indicated in patients who have, like Parker mentioned, AERD specifically make that diagnosis, because it really, I think, provides the patient with important prognostic information and can impact our treatment decisions as well. So we'll focus on that frequently.

Dr. Wechsler:
I think it's critical to obviously step back and take a good history and inquire about all sorts of other symptoms the patients have, and also look from an extra pulmonary and outside of the ENT pathway, what else could be going on, and make sure that you're not missing any other more rare diseases, like eosinophilic granulomatosis polyangiitis that can be associated with sinus disease and lower airway disease, allergic bronchopulmonary aspergillosis, and other entities as well.

Dr. Lee:
Yeah, great points. It's so important how each of the different subspecialties brings a different perspective, and why a multidisciplinary approach really is so helpful, especially for patients who have both upper and lower inflammation.

And identifying inflammation is really key. So going on to the clues from history, as we talked about, we don't have a biomarker for this condition, so we can use some of the clues from history, such as loss of smell that we talked about, nasal blockage, drainage, especially if patients already know that they have comorbid asthma. That's helpful, as well as comorbid AERD. Some of the clues from the endoscopic exam that we use, obviously, if patients have nasal polyps, but sometimes patients can also have this very thick, what we call eosinophilic mucin that is very tenacious and difficult to remove, even with saline irrigations at home and even for us as rhinologists in the office and trying to suction that out of the nose. And you can sometimes even see the little crystals, what we call the Charcot-Leyden crystals in this mucin for our patients who have this severe CRS with NP,.

Some of the labs we talked about. The CBC differential, but especially because of what Mike mentioned with eosinophils, it's important to look at that and see if there's any trends with the eosinophil counts in the blood, as well as serum total IgE. And then, as Katie mentioned, serum specific IgE, but also skin testing for different allergic rhinitis triggers.

This is an example of what a normal CT scan looks like on the left-hand side in a patient who has significant opacification or blockage of all the paranasal sinuses on the other side. And this is a coronal view. But as otolaryngologists, we look at both, not just this coronal view, but axial and sagittal cuts to imagine what the sinuses are doing in relationship to the orbit and skull base in 3 dimensions, especially when we're thinking about surgery too.

Some of the goals of treatment. We want to control inflammation. We want to put out that fire that's happening in the sinuses, and that really helps with hopefully the patient's symptoms. Helps with nasal—the blockage, helps with patient's smell. And also the sinuses, as you can see, is like a labyrinth. So I describe these as auditoriums and like apartments, and each sinus compartment literally has a several-millimeter opening. So to maintain that sinus adequate outflow tract and the ventilation per se, it's really important.

And then if there are any secretions like mucopurulence, it's really important to get—we do get endoscopically-driven cultures. So we're making sure we get the drainage specifically in the paranasal sinuses, for example, in the maxillary sinus or the ethmoid sinus, to really target where the inflammation is happening.

We also want to make sure our patients can have a normal life where we don't have significant exacerbations, whether upper and lower, because, as Mike mentioned, patients who have upper airway inflammation, it can definitely impact asthma exacerbations and vice versa. Patients who have comorbid sinusitis, it's more difficult to control the asthma too.

And then finally, restoring smell is so important. It's one of the most unpredictable things, because we're talking about the cranial nerve I. But, you know, I do counsel my patients that smell is likely one of the most sensitive indicators of the health of the sinuses. And if patients—and I haven't even looked in the nose yet, and when I see my patients and they say they can smell, I kind of have a kind of inkling that the sinuses will also look pretty good.

But I'd love to hear from our patients, Carrie and Parker, on what your goals of treatment are, and what your thoughts are on how you have encountered different treatment options throughout your journey and what has worked for you. So maybe we can start with Parker here.

Patient Parker:
Thanks. Yeah, I think it's initial and ongoing treatment. Like initially, listen, I would have just taken prednisone every day and would have been happy, but apparently you can't do that. And so my case happened to be, you know, a bad one, and so I had to get a—let's, I'm going to butcher this, but a bilateral maxillary antrostomy, sphenoidectomy, total ethmoidectomy, and frontal sinusotomy with Draf III drill-out. So 6 hours. And that, for me, was the initial, you know, step to get back to a baseline of just open sinuses.

And then after working consistently with Dr. Buchheit on, you know, nasal irrigation, COX inhibitors, trying to figure out the right inhaler. And finally, for me, it was the biologic that was the capstone for my care to just get back to normal. I'd say last we've had to sometimes do a dose of prednisone here and there, where I might actually get a cold or, you know, a flare up seasonally, of inflammation that just the normal course of care doesn't work.

So really the goal is get back to that normal, and we had to fine tune where now for about like, 6 years, I've been in a great spot.

Dr. Lee:
Awesome. Great. Carrie, your perspective?

Patient Carrie:
Well, I was only diagnosed this past October. The first thing that we did was I started to use the sinus rinse with a steroid spray, and it helped a little bit, you know, I started to have a little bit of a sense of smell a little bit. I could breathe a little bit out of my nose, but then I started to irritate and there was some bleeding, so that wasn't a good option for me.

And then I have been very fortunate to be involved in a study where I'm taking biologics, and I've only just started in the last month, and I've had amazing responses. My life feels very different, actually. I initially thought it was a like placebo effect, that because I was taking something, that things seemed so much better. But then when I had my latest endoscopy, there really was huge change in my polyps, and my polyps have shrunken significantly. And I'm starting to get smell back. And I didn't even really realize how bad my sense of smell was until I started to be able to smell again.

And it can seem like a really little thing, but I have a couple of examples where it was actually life threatening. We had a gas leak in our house and I couldn't smell it, and my husband came in and he was like, 'There's gas—you don't smell it?' And I could not smell it. My goal is to continue on this study to see if I experience the same amount of relief and improvement. It's just been life changing for me.

Patient Parker:
I could jump in one more on that too. Because the life, it can be an emergency, like externally, like Carrie is talking about. But there's a pretty crazy photo that I shared with the group before we recorded this, which shows, like, my frontal sinuses. And had I not had like, the necessary surgeries to, you know, address this, I could have gone, like, septic or something in my brain, which is crazy. So, like, this is not just, oh, they're like, kind of sniffly, like, you could burn your house down, or have, like, brain damage, like, this is like, really consequential stuff that, you know, these, you know, therapeutics that we're talking about today can make a huge impact on.

Patient Carrie:
And Dr. Lee, I would just add another is that, you know, getting a good night's sleep, you know, everyone knows research just shows how important that is. And, you know, I teach elementary school children, and so I have to have a lot of energy, and I was just feeling so tired, and I feel like I have a new lease on life. You know that I wake up and I'm not exhausted, so it's pretty amazing.

Dr. Lee:
Yeah, that's wonderful. Sleep is so fundamental to health, so being able to breathe through your nose, but also just not have that inflammation raging through your body, I think that's critical, also for asthma too. Thank you so much.

I wanted to talk a little bit more about some of the conventional things I think Carrie mentioned as well, and Parker mentioned intranasal corticosteroids. But there can be limitations, especially with epistaxis or bleeding from use of them. Although they are pretty well tolerated in most people, but a lot of folks, it's just hard to do something twice daily, you know, on a regular basis for a long-term period.

Oral steroids, we really try to avoid if possible because of the cumulative toxic effects. Even one study that was really great looked at asthma patients, but even a dose as low as 500 mg in a lifetime was considered to have detrimental effects in many different areas of the body. So I've been much more cautious. Even as a surgeon, if I'm going to the operating room with the patient and the anesthesiologist wants to give steroids for nausea, I'm like, no, if we don't need to give it, let's please not do it. So I think all of us, I'm sure Katie and Mike included, are trying to be better about being better stewards for oral steroid prescriptions and treatment.

Antibiotics—also, many years ago, there was a thought that this condition was related mainly to bacteria or fungus, but we know it's much more complicated than that. So antibiotics can be used for acute exacerbations, but we don't routinely use those medicines unless we're thinking about different endotype, which is a different presentation altogether. So I won't go into that.

Saline rinses. We do counsel patients a little bit differently how to do rinsing, because it can be really difficult for patients who have polyps. Imagine if your nose, as you saw in the video, was so blocked with polyps to really be effective at getting the rinses through. And some patients say, 'Oh my gosh, you know, the saline rinse got stuck, and I don't know where it went.' And so it can be quite challenging. So we do a lot of counseling in the office on how to do the rinses in a gentle way.

And then finally, we have functional endoscopic sinus surgery, as Parker mentioned. Sinus surgery is a good option for patients who—really, it's a patient preference, it's safe, it's done widely throughout the United States. And also, we now have fellowships where now we have subspecialties like rhinology, where we do additional training for the safety of functional endoscopic sinus surgery. So just a well-tolerated option. Patients do quite well with sinus surgery too.

But we still don't know which patients are the best patients to start a biologic up front, versus someone who needs sinus surgery up front, versus both. And we can talk about that more in a little bit more detail as we keep going with these treatment options.

And the goals of sinus surgery and the indications really are, we want to restore the outflow tracts for the sinuses, remove the polyp

tissue. And we often get to this point in discussion when patients say that they've tried all these things, including the topical rinses and the topical steroids, and even they've been on oral steroids and other medications like anti-leukotriene inhibitors, and they're still really symptomatic, or their asthma is getting worse. So sinus surgery, it's an option, but I'm very transparent, and I think a lot of our community—our otolaryngologists, are pretty clear, hopefully, that this is also it's not—like, I tell patients, this is not like an appendix that's removed. This is not a cure. It's a means to allow for better access for topical drug delivery, and also for patients to rinse, be able to irrigate out the sinuses themselves. So it's definitely an option.

The problem, though, is some patients have really high rates of recurrence, as you can see here. In one study, there was at 6 months, 35% recurrence. At a year, 38%, and even 18 months, almost 40% of patients have recurrence of polyps. So that's something to consider. So we need to be very selective about who we offer surgery to, and be very thoughtful. And then discuss with the patient. We talk about shared decision-making, but that really is so important, to involve the patient, all the options, the pros and cons of all therapies.

And then one of the goals of surgery, as you can see here from a schematic, is to restore these outflow tracts, where you can see this maxillary sinus here, where the outflow tract is obstructed and how after sinus surgery, then mucociliary clearance is now restored, and patients are also able to apply their topical medications to the paranasal sinuses more effectively.

Another study showing the recurrence after sinus surgery in over 34,000 patients. So as you can see here, you know, as surgeons we really hope that the patients, if they need sinus surgery, it's only one good sinus surgery where we say it's a complete sinus surgery, where the ethmoid, the sphenoids, the maxillary, the frontal sinuses are all beautifully open. The patients can access all of them with their rinsing and the topical medications. But unfortunately, that's not the case, and sometimes, and so what we call revision rate, patients even undergoing second sinus surgeries, up to 26%—quite a lot. So hopefully in the future, it'll be 0% but it is reality.

And in patients who have AERD, as I showed in the prior slide, patients can have undergone sometimes even 5 or 6 sinus surgeries, and we really want to avoid that. And the patients who have the elevation of type 2 disease, and if we can identify those, those are the patients who have potentially the recurrence, including the patients with asthma and AERD.

Moving on to some of the very basic tenets of medical and surgical management, is that this is the US consensus published in 2021 showing that, in general, that the consensus is that the majority of patients should do well with a good complete sinus surgery. Obviously, this is decided on between the patient and the physician and the multidisciplinary team with co-management of asthma and allergies.

And then you can see all the different options too, for post-operative management and the different medical therapies, including—and I don't think we've talked about it—but before the biologics were available, we did a lot of aspirin desensitization.

We would do the surgery before, and then about 6 weeks after the sinus surgery, the patients would be started on aspirin desensitization protocol, in conjunction with our AERD colleagues who specialize in AERD. But there are many different options that you can see here for persistent disease.

And this also alludes to the fact that dealing with polyps can be quite challenging because they keep coming back, and sometimes just patient adherence to doing a topical rinse and a spray every day, twice a day, can be quite challenging.

And the final thing. The minority of patients, as we said here, if there's also a contraindication to surgery, or they just don't want to have sinus surgery, then a biologic can definitely be an option for those patients.

So now I'm going to hand this off to Dr. Mike Wechsler for the role of biologics and CRS with NP.

Dr. Wechsler:
Thanks so much, Stella. It's so important that we have so many new options for patients with CRS and nasal polyps, and it's really exciting that we can make a huge difference in their lives.

But the first thing that I think it's important is to try to figure out how to decide which therapy for which patient. And in order to do that, I think it's important to recognize how heterogeneous these diseases are, and that there are different types of chronic rhinosinusitis with and without nasal polyps. And so to appreciate that, I think it's critical to evaluate the specific endotypes. And it's important to ask, what type of chronic sinusitis does this patient have?

Now, we recognize that there are multiple inflammatory endotypes. And we generally think about them in terms of their different cytokines that are involved, the source cells, the effector cells, the immune targets, as well as specific clinical features. And that allows us to offer the potential clinical treatments.

In general, we think of type 1, type 2, and type 3 endotypes, and then there's a group of patients who don't have features of any of

these, who are somewhat undefined.

Now, in the type 1 patients, we think that the primary cytokine that's involved is interferon gamma—it's a Th1-mediated process which also involves innate lymphoid cells, or ILC1 cells, and involves natural killer cells and macrophages. It usually targets viruses, and yet we don't have any good biologic treatments to date, and it's hard to define these patients other than the fact that they have viral infections.

The type 2 patients are really the ones that have been most recognized as responsive to not only corticosteroids, but also the currently available biologic therapies. When we talk about type 2 inflammation, we're referring to inflammation that's mediated by interleukin-4, interleukin-5, and interleukin-13, that's derived from Th2 cells as well as innate lymphoid cells 2, ILC2 cells. These usually involve eosinophilic inflammation, allergic inflammation, and it can be in response to different allergens or parasites, and is associated with nasal polyp formation.

The third type, or type 3 inflammation, is thought to be mediated primarily by interleukin-17, delivered by Th17 cells and innate lymphoid cell 3 types, ILC3 cells. Neutrophils are primarily involved. And we see this in response to different bacteria and fungi. Many of these patients have pus in their upper airways. And for those patients, we really want to offer them antibiotics.

For the patients that don't have any of these features that are undefined, really, we're still trying to learn more about what constitutes the inflammatory processes in those patients.

Another important component is the differentiation between chronic rhinosinusitis with nasal polyps and those without nasal polyps. So we can identify patients clinically as having nasal polyps or not having nasal polyps. But you can see from this study the heterogeneous mechanisms that are at play across a broad group of patients with chronic rhinosinusitis, we see that type 2 inflammation is quite prevalent. That's primarily prevalent in patients who have nasal polyps, whereas in patients without nasal polyps, there's a lot more—many more mechanisms that are involved.

And many patients also have a mixed phenotype, either with type 1 and type 2, type 1 and type 3, or type 2 and type 3. Still, many patients, particularly those who are chronic rhinosinusitis without nasal polyps, are untypable, and they have undefined inflammatory processes that are at play.

When we think about these mechanisms—the type 2 or the type 1, type 3 and the mixed endotypes—we're really referring to all these different pathways that start at the airway epithelium. The upper airway epithelium serves as the first barrier of defense against different pathogens, pollutants, bacteria, and different allergens. And what happens is, is that these different stimuli interact at the epithelial layer, which not only serves as a physical barrier, but also plays an important role in terms of mediating downstream inflammatory processes.

The epithelium makes a variety of cytokines themselves, or epithelial cytokines, also known as alarmins, such as interleukin-25, interleukin-33, and TSLP, or thymic stromal lymphopoietin. We're going to hear a little bit more about the role that these cytokines play, but it's critical to appreciate how different type 2 endotypes, type 1 and type 3 endotypes are from one another and all the pathways that are involved. Because as you can see here, the type 2 patients really have a prevalence of IL-4, IL-5 and IL-13, that play a role more in terms of promoting allergic and eosinophilic inflammation, whereas the type 1 and type 3 patients have more role of macrophages and neutrophils activating inflammatory pathways.

As I mentioned, many patients have mixed endotypes with features of both type 2 and non-type 2 inflammation that can result in the inflammatory processes that we see, as well as potentially tissue remodeling.

Why do we need to know all of this? Well, the reason it's important to understand the different endotypes, the different mechanisms, is because now we have available a variety of therapeutic targets. We have tezepelumab that works upstream, that can target TSLP and prevent some of the downstream activation that we see in terms of some of the type 2 inflammatory processes, because TSLP is involved in activating innate lymphoid cells and Th2 cells to produce IL-4, 5, and 13.

Further downstream, we can target specific cytokines and the receptors of those cytokines, so mepolizumab, benralizumab, and depemokimab target IL-5, or the IL-5 receptor, and play a role in terms of abrogating eosinophilic inflammation.

Dupilumab targets the IL-4 receptor and plays a critical role in terms of preventing a lot of the other type 2 inflammatory processes. IL-4 binding prevents B cell activation and production of IgE, which binds to mast cells and plays a role in the allergic inflammatory process by developing and activating production of histamines, tryptase, prostaglandins, and leukotrienes, amongst other things, that can cause inflammation in allergic patients.

Furthermore, IL-13 is also involved in inflammatory cell recruitment, mucus production, and airway hyperresponsiveness. So dupilumab plays a role in terms of preventing a lot of the allergic and inflammatory processes that go on in the lower airways.

Lastly, omalizumab has been approved for chronic sinusitis because it binds IgE and prevents IgE from cross-linking on the mast cell and basophil and prevents some of the allergic inflammatory processes.

So it's exciting that we have all of these therapies, and I'm going to pass this on to Dr. Buchheit, who will go over the different therapies and the data that have led to their approval in patients with chronic rhinosinusitis. Katie?

Dr. Buchheit:
Great. Thank you so much. So we are going to talk now about the three biologics that are US FDA approved for treatment of chronic rhinosinusitis with nasal polyps. Dupilumab, which is approved in adolescents and adults, and then omalizumab and mepolizumab, which are approved in adults. And then we're going to talk about some data from the phase 3 studies of two drugs, depemokimab, which is an ultra long-acting anti–IL-5, and then tezepelumab, an anti-TSLP, which are not yet approved for treatment of chronic rhinosinusitis with nasal polyps. But the new data is really certainly interesting to review in this context. And I will say that benralizumab has been studied for chronic rhinosinusitis with nasal polyps. And the results of the initial phase 3 study were published in 2022, and then there's going to be forthcoming data with a second phase 3 study. So more to come there.

But first I want to introduce the concept that there are some limitations of indirectly comparing these different studies. There are some important differences to note in enrollment criteria, the sample size of the studies, certainly treatment duration.

And just to point out some, I think, key differences among the trials—notably the POLYP 1 and POLYP 2 studies, which looked at omalizumab for treatment of chronic rhinosinusitis with nasal polyps compared to placebo—there were fewer patients who had a history of prior systemic corticosteroid use compared to the SINUS-24 and 52 studies, which looked at dupilumab compared to placebo for chronic rhinosinusitis with nasal polyps. And then also the SYNAPSE study.

And then, importantly, all of the patients who were enrolled in the SYNAPSE study, which looked at mepolizumab versus placebo, had a history of prior sinus surgery, whereas not all patients in the SINUS-24 and 52 studies and the POLYP 1 and POLYP 2 studies had had a prior sinus surgery.

Notably, there are a lot of similarities in the enrollment criteria. All the patients had to have a bilateral Nasal Polyp Score of greater than 5 out of 8. So they had pretty substantial nasal polyps burden. They were all on a background of intranasal steroid.

So looking through here, everything is actually color-coded going forward. So all of the data for each study is kind of presented in the same colors here, which you can follow along with. Some, I think, important key information. These are the three US FDA approved biologics: dupilumab, omalizumab, and mepolizumab. And the dosing for these is either Q2 weeks or Q2 to 4 weeks for omalizumab, based on patient weight and serum IgE level; Q4 weeks for mepolizumab.

Generally these are, you know, reasonably well tolerated, and, you know, these are highlighting some really kind of key secondary endpoints that were investigated in the studies, looking at, you know, for dupilumab, improvement in sinus opacification, which we'll actually look at a representative CT scan; for omalizumab, there was a reduction in need for systemic steroid, need for surgery; and certainly in the mepolizumab study again, 42% lower need for systemic steroid, 57% reduced need for surgery.

And then for the agents under investigation: depemokimab, this is a little bit different. The dosing is every 26 weeks, so different than the other drugs that we've talked about. Tezepelumab, the dosing is every 4 weeks. Again, these are well tolerated in terms of adverse events, very similar to placebo. And important secondary endpoints to note—in depemokimab, there was between depemokimab and placebo a nonsignificant difference in need for surgery, but there was a 42% reduced need for systemic steroid. Tezepelumab, there was a 98% reduced need for surgery and an 88% reduced need for systemic steroid.

So, you know, just to highlight the clinical trial outcomes, the studies of dupilumab, omalizumab, and mepolizumab all demonstrated improvements in the co-primary endpoints: Nasal Polyp Score, the measure of nasal congestion, patient-reported nasal congestion, as well as improvements in SNOT-22 scores. And then some of the studies—and we'll look at this more closely—also evaluated objective measurements of smell identification, looking at the UPSIT test.

So this here is really a study where they brought together the relevant data from the phase 3 RCTs. So this is a synthesis of data. It's not a meta-analysis. There was no formal assessment as to heterogeneity or weighting of the studies. But I think it, you know, can be a helpful way to sort of visualize some of the differences in the studies that we see.

So looking at the phase 3 results in terms of the Nasal Polyp Score—so endoscopic nasal polyp burden—we see that in the two dupilumab studies, the SINUS-52, SINUS-24, and then also the WAYPOINT study looking at tezepelumab, that there is, you know, around a 2-point decrease compared to placebo in the Nasal Polyp Score, which, you know, is different than what we're seeing from the studies of omalizumab, mepolizumab, and depemokimab.

Moving along, looking at again the UPSIT score, which is only done in the studies of omalizumab, dupilumab, and tezepelumab for chronic rhinosinusitis with nasal polyps. This is a scratch-and-sniff evaluation, and we see that, you know, there's pretty similar efficacy in terms of both dupilumab and tezepelumab. And certainly treatment with dupilumab and tezepelumab led to identification of more scents than did omalizumab, looking at this here.

And then lastly, looking at SNOT-22, which is really a quality-of-life measurement, we see that there's really kind of considerable overlap in the 95% confidence interval on these forest plots between all the agents, with most of them exceeding the known MCID, or minimal clinically important difference, of about 9. And there were some important baseline differences in SNOT-22 scores at enrollment. This is another area where it's important to look at kind of the enrollment data. Patients in the SINUS-24 and SINUS-52 studies had a baseline SNOT-22 score of about 50 at enrollment, compared to the WAYPOINT study, where it was about 69 at enrollment. So certainly differences in heterogeneity in the patient populations could be influencing some of these results.

Moving into some of the specific primary endpoints for the different agents that are approved. These are the results from the SINUS trials of dupilumab compared to placebo for patients with chronic rhinosinusitis with nasal polyps. And we see that there is actually pretty quick improvement in both the Nasal Polyp Score—so the endoscopic measurement of nasal polyp burden—as well as the nasal congestion or obstruction scores.

In the SINUS-24 study, the drug was stopped at 24 weeks, and we see that off treatment that the Nasal Polyp Score increases, as does the nasal congestion score. In patients in the SINUS-52 study, where it was continued for 52 weeks, we see ongoing improvement. So, you know, these, you know, results show that, you know, this is quite efficacious for patients with CRS with NP.

And looking here, this is a pre- and post-treatment CT scan, we see that there's substantial reduction in inflammation in the paranasal sinuses with treatment with dupilumab.

Moving along, looking at the POLYP trials, which looked at omalizumab for CRS with NP, we again see that there is reduction at 24 weeks in the Nasal Polyp Score, and then mean change from baseline in nasal congestion score as well compared to placebo. Again, this is a really shorter study than the SINUS-52 study, but we see that there's pretty quick improvement. Really, at 8 weeks patients are starting to feel better.

Looking at the results of the phase three study for mepolizumab—so anti–IL-5 compared to placebo, the SYNAPSE study—this data is displayed in a somewhat different way, looking at a little bit more idea about the heterogeneity of response that we're seeing to the drug. But there, you know, is a substantial percentage of patients who had improvement in their Nasal Polyp Score, and then also improvement in their nasal congestion as well. So, you know, this certainly works for some patients with CRS with NP. And I think kind of thinking through the mechanistic information that Dr. Wechsler presented kind of helps us get a sense that, you know, IL-5, and inhibiting IL-5, certainly has a substantial impact for specific patients. And further being able to identify those patients will help in terms of personalizing treatment down the road.

And then the last two studies we'll look at are the drugs that have been under investigation. Depemokimab—again, this is the ultra long-acting anti–IL-5—we see that at 52 weeks, there is improvement in both the Nasal Polyp Score and then also patient-reported nasal congestion compared to placebo.

And then, to wrap it up, the results from the WAYPOINT trial looking at tezepelumab compared to placebo. We see again, a change from baseline compared to placebo in terms of Nasal Polyp Score and improvement in nasal congestion as well, as well as some of the secondary endpoints that we already talked about, including smell identification, need for systemic corticosteroids, and need for surgery.

So it's a little bit of a whirlwind, and I'm going to hand it over to Stella, who will tell us about a little bit of head-to-head data that's available now.

Dr. Lee:
Great. Thanks, Katie. Thanks, Mike. I know that was a lot of amazing but very complex information, but thank you for breaking it down for us. It was really great to understand all the different outcomes and what was studied.

There have been a lot of network meta-analyses of different biologics, comparing them against each other. But this is one of the first head-to-heads. Actually, it is the first head-to-head study comparing two biologics, dupilumab versus omalizumab, in patients with CRS with NP. And as you can see, for the Nasal Polyp Score, there was an improvement or difference between dupilumab versus omalizumab—dupilumab is in the magenta color and oma in the green color. The difference between the two is about 1.6, so pretty significant for the difference in improvement in Nasal Polyp Score between the two.

So moving on to the smell outcome for specifically UPSIT as well, it looked like dupilumab also performed better here with an UPSIT

score, as you can see here, difference of about 8 between the two, although it does also look like omalizumab had some improvement as well.

And then if you look at SNOT-22 scores, which is the really important patient-reported outcome measure that we utilize, Sino-Nasal Outcome Test, it does also look like—which is great—it looked like both biologics do help patients feel better, but it did look like dupilumab performed a little bit better here, about 12.7 point difference compared to omalizumab.

So going back to our faculty panelists, I wanted to chat with you a bit about how you select treatment. You've presented all of this data, and so what factors would you consider? Maybe we can start with Mike. How do you process all this biologic data? And when you have a patient who is in front of you who has CRS with NP and comorbid asthma and allergic rhinitis, or plus or minus some of these comorbidities, how do you decide? And if you could you talk about that, that'd be great.

Dr. Wechsler:
Yeah. So first of all, it's important to use shared decision-making and have a frank discussion with patients regarding frequency of dosing, access to medications, cost of medications. So that's part of the discussion.

And then what I focus on primarily is, what type of disease do they have? What type of CRS do they have? What type of asthma do they have? And I'm going to look at the biomarkers that they have. Is there a specific dominant biomarker? Do they have a mixed endotype? And what are the different options for our patients? And also, do they have other comorbidities that I can try to address with the specific biologic therapies?

So for instance, if the eosinophil count is way out of proportion, a dominant biomarker, you know, 800, 900, 1000 cells per microliter, I'm much more likely to give an anti–IL-5 therapy. If the exhaled nitric oxide is markedly elevated, then I'm much more likely to give an anti–IL-4/13 therapy. And if there isn't a single, specific dominant, then I'm going to look at the relative data for each of the different biomarkers and for each of the different therapies, and see what is best for my patient. Take into consideration all the other patient-related factors that they may consider to be important as well.

Dr. Lee:
Yeah, thanks Mike for sharing that. Katie, your thoughts? And how do you decide? And then, what would you consider a successful treatment?

Dr. Buchheit:
Yeah. So, you know, I do a lot of the same things that Mike does. So I think that doing endotyping is really helpful. I like to do that actually up front when I initially meet the patients, before we introduce any therapies. Because, you know, all of those variables can be affected by treatment with biologics, systemic corticosteroids, and even sinus surgery. So I'll try to do that as early as possible to get a sense of what's driving the patient's disease.

And then, you know, as Mike said, we think a lot about comorbidities. There are a lot of conditions that we manage in allergy and immunology that can be, you know, successfully treated with biologic therapy. So we think about things like comorbid atopic dermatitis—you know, those patients, I would often choose something like dupilumab. We think about comorbidities and esophagitis, we treat that. We treat a lot of comorbid urticaria. So, you know, trying to choose a biologic that will help the patient in as many avenues as possible is, I think, really important.

And then in terms of, you know, identifying successful treatment, I'm looking for, you know, reduction in need for medications—you know, specifically systemic or oral corticosteroids—also reduction in need for revision sinus surgeries, and improvement in quality of life. You know, patients generally feeling better, sleeping better, improvement in sense of smell. And, you know, we do less in terms of measurement of nasal steroid burden. I, you know, send those patients to see you to death. But, like, certainly, we love hearing reports that patient sinuses look great and that, you know, they almost have normal sinonasal mucosa after treatment.

Dr. Lee:
Yeah, great. Thank you so much for sharing that. I think that's so important to have that conversation among our multidisciplinary, you know, team to assess how patients are also doing. And we all have different ways of looking at patients from our respective fields.

Going back to some of the basics, as Katie and Mike mentioned, some of the indications for biologic treatment for the biologics that are currently available for CRS with NP—some of these are pretty obvious—you know, evidence of type 2 inflammation. Sometimes we can look at eosinophilia. It looks like perhaps tissue eosinophilia is probably a better way to assess the evidence of type 2 inflammation, but then again, blood eosinophils are also helpful.

We can look—and these are not set in stone, these are suggestions. So you can see there's total IgE levels here. Need, or I think more important here is whether patients respond well, and they feel better, their asthma is better, their polyps shrink on systemic

corticosteroids—that can be, you know, an indicator that the patient would also benefit from being successful in treatment with a biologic. Patients have impaired quality of life—those patients who are really having impairments in their sleep and their breathing, in many different subdomains that we look at. So SNOT-22 can be helpful to make the decision. Patients who can't smell as well, and then the comorbidities, as we discussed.

And then this slide is going over some of the responses. As Katie mentioned, how do we define whether a biologic is working for a patient or not? And these are kind of obvious, but let's go through them just briefly. When we look in the nose, we really do want to see that the polyps have shrunken down and gone away, hopefully. We also want to see that the patients don't need systemic corticosteroids, that they're feeling happy, that their quality of life is improved, they can sleep, they can smell, and that also their asthma is better, their atopic dermatitis is better, their urticaria is better, for example. So this is just a very basic framework on that.

And the one last slide here on disease states. This is something new from the otolaryngology side, and the rhinology side, as well as the folks here who are all working and doing active research on CRS with NP—is how do we define remission? And I know that's been an area that's been discussed in asthma, but we are also trying to understand what remission looks like in CRS with NP. And this is also a suggestion that perhaps remission, we should defined it as no symptoms or endoscopic signs, and it should be active disease at about a year or more, but it can be on persistent treatment. So that is still an area of controversy.

And then, as you can see, we're looking at cure as well, but we are trying to further define what it looks like for not only disease control, but what it looks like for when we can tell patients, Oh, wow, you're in remission from this condition, or hopefully in the future, we can say you are cured from this condition, which would be amazing.

So going to our final key takeaways. We know that this is a very common condition. CRS with NP in particular affects over about 3 million people in the US. There's mainly a type 2 inflammatory endotype, but there can be different mixed endotypes. As we know, there are common comorbidities such as asthma and allergic rhinitis as well as atopic dermatitis. And unfortunately, despite the best that we do, sometimes with sinus surgery, even up to 40% of people have recurrence of polyps, and we need to understand that better. And the risk factors for that recurrence are several. If the patients have comorbidities like asthma, AERD, or even history of prior sinus surgeries, that can be an indicator that they will probably not do well with another subsequent sinus surgery. We don't have a biomarker yet, but eosinophilia, whether in the tissue or the blood, can be helpful. And as Mike and Katie shared with us, all these pivotal trials and other new trials coming up have really revolutionized the way we think about this condition and the treatment of the condition.

And hearing from Carrie and Parker, it's been really inspiring to really understand how it's changed their lives, and it can improve not only these numbers, like we're talking about Nasal Polyp Score and SNOT, but it's really changing people's lives. So that's really wonderful to hear.

I want to thank you so much to our patient panelists, Carrie and Parker, and our faculty panelists, Dr. Buchheit and Dr. Wechsler. Thank you so much. We really appreciate sharing your expertise and your experience and your perspectives. Thank you very much.

Dr. Buchheit:
Thank you for having us.

Dr. Wechsler:
Thanks. This was a great session.

Announcer:
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