

Dr. Mariam Hanna: Hello, I'm Dr. Mariam Hanna, and this is The Allergist, a show that separates myth from medicine, deciphering allergies and understanding the immune system.

I've been known to wave my hands in the air and say, hey, I'm over here. Let's talk about the story and worry less about the size of each test. Or, can we please stop staring at the screen and agonize less over a number when context is more important? Try telling that to my patients over and over and over. And perhaps, to a part of some of my brain, that almost can't unsee a number once it's been done.

What are we going to do in the age of multiplexes that test 300 things in one go? Ah, a story for a different day perhaps. But behind all that is another equally interesting couple of chapters to this story.

I have an infant that was started on dupilumab for severe atopic dermatitis, also had multiple food allergies diagnosed in early infancy. Now, negative blood work, still on the biologic, it's working great. Did he outgrow the allergy? Or are his tests being masked? Cause now I need to figure that out. And what about the patients that have done immunotherapy? How do I figure them out from testing? And why does repeat testing become so routine in the food realm when it's actually not routine in the aeroallergen realm? Interesting, right?

So this time, I put out a public call on social media, it's my first time doing this, and the right person came forward for this conversation, which is really, really exciting, and I think I learned to ask for help from this whole situation. It is my pleasure to introduce Dr. Nicole Chase, she is a nationally recognized physician, researcher, and educator in allergy and clinical immunology. She serves as associate professor of medicine at the University of Minnesota, and partner at St. Paul Allergy and Asthma.

Dr. Chase's clinical expertise spans anaphylaxis, asthma, atopic dermatitis, chronic urticaria, and eosinophilic gastrointestinal diseases, with a focus on, here you go, novel therapeutics and the immunology of atopic diseases, making her the perfect person to interpret all these tests for me now. Her current research focuses on how artificial intelligence can support clinicians and sustain independent specialty practice. Maybe AI will solve all my issues interpreting these tests.

Okay, Dr. Nicole Chase, thank you so much for taking time to join us and welcome to the podcast.

Dr. Nicole Chase: Thank you so much for having me, it is my pleasure to be here.

Dr. Mariam Hanna: Okay, so I was so excited, because we use skin prick tests and serum specific IgE like nobody's business, right? For diagnosis, we talk about likelihood of a reaction, and following patients over time as we see them from one year to the next, whether we're actively intervening on the food allergy specifically or we're just following for its natural history.

Are we asking these tests to do more than they were designed to do? Let's start with that and get your rant.

Dr. Nicole Chase: Absolutely. We have known for a long time that the best data you can collect from a patient visit is the history and the physical examination. And what we've done historically is used skin prick testing and serum specific IgE levels to look at sensitization.

Now, over time, we've developed some of these these different standards, 95% positive predictive values, but these were done in very specific populations, and they do not predict an individual patient's threshold, nor their severity of reaction, and we know this.

So, even with the evolution of molecular diagnostics, component testing, right we all know about Ara h 2, this helps us, but it doesn't actually solve the problem. It's like asking these tests to be a smoke detector for the question really what we're asking is, how big of a fire is ongoing?

Dr. Mariam Hanna: So, are we creating this giant gap between the test result and what happens in the patient encounter?

Dr. Nicole Chase: So I think we really are widening this gap of what we see and what we should actually think about and advocate for the patient to when to be concerned, right? The real goal in the exam room is to give the patient and family guidance, and our tests are becoming less and less relevant for the clinical context that the patient is in.

Dr. Mariam Hanna: That that is basically the conundrum we're going to unravel right now. I I want to take a moment and kind of compare to where we are in aeroallergen. And aeroallergen immunotherapy is much more standard of care, historically done for eons, and we don't we don't do the routine repeat skin test or specific IgE or a chamber challenge for these patients to to prove we've done our job.

Dr. Nicole Chase: I think that it's just because of the differences in exposure, right? So for aeroallergens, we can assess, well, how was last spring for you? How were your symptoms? Did you have to use adjuvant medications? We don't have to do skin testing, because we have clinical data that we're gathering, whether the patient wants to be gathering it or not. They've gone to someone's house where there's a cat, and they can tell us how they've needed to treat themselves or how they feel.

Venom, we we really look at this more of a risk severity, right? We're not stinging challenging people, but we look at how severe their original reaction was. We see whether their tryptase is high or do they have, you know, indolent systemic mastocytosis, what what venom is it? Is it honeybee, right, versus everything else? Are you a landscape architect and outside all the time? And then how did you how did you do during your immunotherapy?

So yes, it would be maybe nice to see a negative test, but we we don't think that the risk stratification warrants it. And so in food, this is where it's really different, because I don't think that we actually agree on what success means.

We look at these numbers, whether it be wheal size, wheal diameter, or whether it be serum-specific IgE or component changes or or decrease of 50% compared with before. Basically, these numbers feel like end points to us, but really the only true end point is what

happens in a challenge. And it's just it's hard to do challenges in that quantity, in that volume for all of these patients, and so this is why we're using the numbers as surrogates.

Dr. Mariam Hanna: And and, like, what to do in a challenge? Extrapolate that a little bit in food allergy, because I I'm cool to do one challenge, but, like, it's also like sustained unresponsiveness, and is it remission? And how long is that sustained unresponsiveness? Can you comment about that as well?

Dr. Nicole Chase: I think we really don't know. I mean, it's this is hard, where all of our data is population data. And yet, in food allergy patients, they really are an n of 1. Are they on other medications? Okay, let's say it's a common food like egg or milk. Well, what degree of heated or baked do they actually tolerate? What's the quantity of food that they've ingested with their oral immunotherapy?

I think that this is why food allergy is so, so complicated is because every single patient is so hyper-individualized. And to your point, physically, it's just very difficult to do challenges with families that are otherwise, you know, maybe anxious, maybe the food is not something that they they necessarily want to be eating regularly. There's just lots more variables, I think, in food allergy than in any of the other allergies that we treat.

Dr. Mariam Hanna: I know. It's made it unique, and it's made it very time-consuming. Let's talk about biologics and small molecules. Which ones have impact on skin testing? Which ones can impact blood work? Does that clinically mean anything? And that's really mean, because I just threw you under the bus with all of these questions. So let's unpack them one drug at a time, if you prefer, or to compare and contrast us.

Dr. Nicole Chase: Sure, let's just start. So, omalizumab is an anti-IgE monoclonal antibody. It's an IgG antibody, so it itself has a half-life of about 3 months. We think that when we give a patient omalizumab, it binds to their free circulating IgE, and that that is why these molecules now last a bit longer. So sometimes people will see an IgE level increase after administration of omalizumab.

We also have learned that the quantity of free IgE directly correlates with the quantity of high-affinity IgE receptors on tissue-bound cells, like mast cells. And so what we think is happening is that by binding the free IgE, we also downregulate the high-affinity IgE receptor itself on the mast cells, and we think that this overall decreases reactivity of those cells.

I I think in general that we've learned a lot about omalizumab from data in other disease states, like asthma, where we may actually be seeing increased concentrations of interferon-gamma, and maybe this is why kids in the severe asthma, you know, Inner-City Asthma Consortium trials actually had improvements in their asthma, not just seasonally, not just when we bound the circulating IgE to pollens and things, but also perhaps were actually downregulating the type 2 immune response and increasing a type 1 immune response with this interferon-gamma production and decreased incidence of viral illnesses triggering asthma.

I'm way off topic from food allergy already here, but at the same time, that's kind of how I think about omalizumab. You lose the specific IgE as a biomarker as soon as you start to administer the drug.

Dr. Mariam Hanna: Okay, so the food-specific IgE or the allergen-specific IgE, you lose that biomarker. Your total free IgE goes up potentially in some patients, and then what happens to your skin tests?

Dr. Nicole Chase: So your skin testing in general will decrease, although some patients will still see some degree of skin reactivity. And this is where it depends on, you know, what the actual dose of the drug, that how long the patient has been on the drug, and and, you know, when their last administration was. We know that protection will wane over weeks to months.

In asthma, we see that when patients stop omalizumab, I always call it a honeymoon, where their asthma might be fine for 6 to 9 months after their last dose, and then we see an increase in symptoms. I think for food allergy, we have yet to understand this about what happens to someone if they've otherwise been on omalizumab and then stop.

I think that at least in the OUTMATCH trials, it appears as though you start to react, those kids that had started with omalizumab and OIT, and then discontinued omalizumab, you did see that more of them would start to react as the drug wore off.

Dr. Mariam Hanna: Okay. And can you comment about how long that honeymoon period could be when it's used for food allergies specifically? Is it still that 6 to 9 months, or is it, like, 3 months, for example, like the buildup phase?

Dr. Nicole Chase: Yeah, I think it's sooner. I think that there was data from the I think it was phase 2 OUTMATCH, where you saw that people that were just free-eating the food, that, you know, they measured it at 3-month intervals, and so you saw even at, you know, 3 months that fewer numbers of individuals could tolerate the same quantity of food, and that number just kept going down the longer they were off the drug.

Dr. Mariam Hanna: Okay, so as early as 3 months. So then now the next biologic. Okay, so let's go to dupilumab, because that one, again, incorporation in infancy is is clouding my judgment or making it trickier to say, is this a patient that has naturally resolved their allergy, or is this being messed up because I've put them on dupilumab? So let's talk about what happens there.

Dr. Nicole Chase: Okay, so dupilumab, the mechanism of action, it's an anti-IL-4 receptor antagonist, and the idea here is that because the IL-4 receptor is shared by both IL-4 signaling and IL-13 signaling, that you actually are blocking both pathways. The way I think about it, historically, I thought it was really mostly IL-4. There's some recent data to suggest that it may be very much IL-13 driven, but the concept is is that you need to have the presence of 4 and 13 to induce class switching, back to basic immunology, right? You have to go from IgG to other isotypes, and so we want to class switch to IgE. So if you block that process, you're going to actually block the induction of type 2 shunting to produce IgE.

So we see that in data that's been published, that total IgE goes down after initiation of dupilumab. It's not immediate, like we see decreases in eosinophil counts or maybe in FeNO levels, but you do watch over time that trend gradually go down. And this is true also for serum-specific IgE, whether it be aeroallergens or whether it be foods.

So to your point, I agree with you that the testing that we do for our patients, I will still frequently skin test patients that are on dupilumab and omalizumab just to see maybe where they're at, but I think that it begs the question of, do these patients all really just deserve a challenge to know, because our data now is skewed?

Dr. Mariam Hanna: Okay. And so as we said, total is not reliable and often goes to negative over time. Serums or food-specific again can become negative and shouldn't be relied on. Yes, go ahead.

Dr. Nicole Chase: Yeah, I just wanted to make a point also where, you know, I think that we think about total and serum-specific a lot in food, but one other place to be very, very aware is that we use total IgE as a marker for fungal sensitization. So ABPA, right, classic example.

I had a patient recently where they were on dupilumab for their nasal polyposis and still just very, very symptomatic with their asthma, despite initial good clearance, good improvement in FEV1, decrease in exacerbations, and come to find out, I think this patient has ABPA, but I didn't realize it because their total IgE was suppressed.

So reminder to think about IgE, it is an effector molecule, it does mean something, whether we understand it or not. You know, we see this a lot, IgE is elevated in severe atopic dermatitis, but remember, there are other disease states for which IgE is an actual diagnostic component.

Dr. Mariam Hanna: An excellent immunology reminder, actually. You know, I find that as we use more biologics, we need to remind our brain more of that basic immunology knowledge, because we're implementing it in practice.

Now, okay, I'm trying to figure out what to do with this patient. If I challenge them on dupilumab, am I really getting the right result, or is that the honeymoon period, because eventually perhaps this infant that was started will stop this biologic, and I'm giving them the wrong recommendation? What do you do there?

She's shrugging her shoulders for the audience that's listening.

Dr. Nicole Chase: I wasn't supposed to have all the answers, just the explanations. So I agree with you. I think that you have to put an asterisk by the result and say, this was the result on dupilumab. This was the result on omalizumab. And I think that that's all you can effectively say is, this was the context in which we tested you and then challenged you.

And so this is all I can tell you is, if you remain, quote, unquote, the same, then this should be the expected outcome. If you skip doses, if you go off the drug, if, you know, I even wonder about this in terms of omalizumab. What if your weight increases significantly, and I miss it and

don't increase your dose? I don't know what people are doing about this, but I do think that in general that we absolutely cannot predict the future in terms of if you're doing anything different than what you're doing today.

Dr. Mariam Hanna: Okay. Now, I think I would like to say, like, you know, in my practice, perhaps omalizumab and dupilumab are the two most frequently used within my food allergy population, so that's probably where I've run into this issue the most. But these aren't the only biologics, and we're continuing to see some new biologics get interest in the food allergy space.

Can you make a comment about specific ones or general ones that you think we should comment on at this day and age?

Dr. Nicole Chase: I think that what's most interesting are the mast cell drugs. So these are going to be things like remibrutinib, things like barzolvolimab, right, briquilimab, where you actually are targeting the mast cell itself as the effector cell. If we can actually decrease reactivity of mast cells, either by blocking their activation or perhaps inhibiting their survival or perhaps even depleting them entirely, that these are looking very interesting in the food allergy space.

I think that this is going to pose an additional can of worms for us, because, you know, we have to think about when we're giving a drug, a biologic is a very large molecule. You have to give it through an injection. You can't get it into the body. Whereas these, quote, unquote, small molecules are exactly that. They're small enough that you can actually ingest them orally, and they'll still be effective without being degraded.

I think that it really begs the question of, every time we're giving these, we are giving these in a method that is systemic, but not exactly in the tissue that we want to look at, right? So it's not actually being delivered to the skin of the patient. It's not actually being delivered to the gut in the same way that let's say applying a topical might for for a patient.

So I think that we're going to be forced to consider these same questions with these newer biologics. However, if we can actually prove that the depletion of the mast cells or the mitigation of the mast cell activation really does decrease throughout the tissue, I think then we can think about, okay, maybe our skin testing will actually predict if a negative will mean a negative for an actual clinical challenge, but remains to be seen.

Dr. Mariam Hanna: Okay. And IgG4 testing, so I get that this is only done in research settings, but if it was clinically available to allergists, would this be an end point that we could follow to say that they have increased tolerance to a food, or would this also still mess us up?

Dr. Nicole Chase: I mean, I think in general that, yes, it's another piece of data. I'm not certain how helpful it's going to be, right? Like, do you need to have a certain ratio of the IgE and the IgG4? We think that that proves response, right? Something is happening. We've seen this years ago in our aeroallergen trials. You decrease your IgE, you increase your allergen-specific IgG4, but it doesn't mean that the patient is safe. It's a different question than what we're asking clinically.

And so I think that, you know, we're looking at this, basophil activation testing, mast cell activation testing, these are even more perhaps promising, but still not ready for prime-time routine clinical use.

Dr. Mariam Hanna: See, so I was trying to get away from what is ready for prime time, which is oral food challenges. And you talked about lots of barriers to them and risks and, time is the other one that many of my adolescents complain about, missing a whole day's worth to attend clinic for this.

So how do we balance their value against their limitations? If we're going to do the test, but we have this like bright asterisk beside it, and say, with all these provisions, are we actually helping them? Does this actually help them in clinical care or not?

Dr. Nicole Chase: I think it absolutely does. But I think that it really, really begs the question of, what kind of outcome would move the needle for a patient, right?

I find myself doing many more of these challenges to like a quarter teaspoon of peanut butter, right? I just want to know that you've now, A, tasted it for once in your life. For these little kids that have never even had necessarily exposure, they don't remember what peanut butter tastes like. They're terrified of the smell. They're terrified of their friends near them.

Great, let's try feeding you a small amount, so that if you ate a cookie that you thought was oatmeal raisin and it turned out to be peanut butter, you would know what the taste is, you would know that you are otherwise on therapy to try and decrease your activity, you could spit it out and notify an adult.

I think it really depends on, do you want to do a challenge per the standard guidelines, 8 g, go for broke, or is maybe a smaller, maybe fewer step oral food challenge actually going to provide better quality of life, decrease your anxiety, maybe increase your dietary freedom? What do you actually need right now? I think that not everybody needs a double-blind, placebo-controlled, standardized oral food challenge like we used to do them to decide if someone was truly allergic or not.

Dr. Mariam Hanna: And why do we not have the same demands of aeroallergens or venom? Like why why is history and clinical response enough? Like severe reaction in venom, I mean, you're you're on it for life regardless of how well you think you've responded or not. Why is this question I know I'm bringing you back to this, but I want to push you a little bit on this one.

Dr. Nicole Chase: I just think that there's no surrogate for food, right? If we had an ideal biomarker that would tell you the threshold, the severity, how you would do regardless of therapy, right? Aeroallergens rarely kill people, and the symptoms that patients tell us about, like, well, that's good enough, we think, right?

Venom, if you really want to test it, someone you just wait until they get stung again and see how it goes, right? We're not great at identifying the allergens or the venoms, but at the same

time, like, okay, people do sting challenges and whatnot, and we have data that's been done historically on that.

There's no good proxy for food. We have to have patients eat the food to decide what's happening, because back to the original point, you can get all of the data you want, but it just doesn't tell you the actual outcome that patients need to know about, which is how severe, et cetera, et cetera. There are too many variables, and it's too high stakes for us to just leave it to chance.

Dr. Mariam Hanna: Too high stakes. Now, the last question is, because you like thinking in in novel research and AI space and things like this, so if there's one thing that we can change about interpretation of allergy tests, and feel free to incorporate technology or not incorporate technology in this, in the disease-modifying treatment era or just in the interpretation of lots of data where we're ambushed with more numbers than we want to see with some of the newer technologies, what would you change first?

Dr. Nicole Chase: You know, I think that even though I love AI, right, I'm coding every day now, like a complete nerd that I actually am inherently, I love it. I think that I would really go back to basics, and I would say, what does the test change based on the result? What are you going to do? I make myself in every clinical visit, I bet, right, in my mind.

But I feel like all of these tests are useless without a pretest probability, a positive predictive value. This is why it doesn't matter even if we get better tests, we have to think about what is this going to mean for the patient? What am I going to do with this, right? Think about the treatment and understand, oh, because of this, this may change. Okay, this all it does is it changes your positive predictive value, your pretest probability.

This is why AI is not going to replace clinicians, because we understand the patient and the patient's own variables, and, you know, economics in terms of what they value, what they are against, et cetera. The tests are only there to help us decide what best guidance to give to the patient. They're never going to be the same as what happens when the patient is out there in the real world, especially in terms of foods.

Dr. Mariam Hanna: Perfection. All right, that's it. That's your final statement. Time to wrap up and ask today's guest, Dr. Nicole Chase, for her top three key messages to impart to patients and physicians on today's topic, the testing of allergies and diagnostic dilemmas. Dr. Chase, over to you.

Dr. Nicole Chase: Okay, number one, sensitization is not a diagnosis. Even though a test changes, this does not mean that the patient is cured. Allergy tests are evidence toward a verdict, but they are not the verdict themselves.

Number two, you need to understand immunology. We are not just allergists, we are allergist-immunologists. We say this for a reason, or or allergologists, immunologists, we need to understand the mechanism of all the medications we prescribe, not just because it helps us pick the right drug for the patient, but because every single test we do as a result is going to be

modified by that mechanism in one way or another. And each therapy has a different point in the immune cascade where it works, and so the same test result in a patient can mean very different things when you consider what their context is. This is the importance of understanding the pathophysiology and the pharmacokinetics of drugs.

And three, I am huge into empowering patients. I want them to I want them to define success the way they need it to. Is it a higher threshold for food? Is it fewer reactions? Is it just that food allergy takes up less mind space in your mind, or that it's you're less worried when you live in the world? We need to define success the way patients live it, and then we have to prove it, and prove that it lasts. We need to have the same standard for food allergy as we do for venoms and aeroallergens, it just may require a bit of a higher bar to define that success for the patient.

Dr. Mariam Hanna: Brilliant. Raising the bar, I like it. Thank you, Dr. Chase, for joining us on today's episode of The Allergist.

Dr. Nicole Chase: Thank you so much for having me. It was a delight.

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