Improving Anaphylaxis Outcomes: Approaches for Enhancing Access to Epinephrine

December 16, 2025

Workshop Transcript

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Valerie J. Parker:

And welcome to today's meeting, Improving Anaphylactic Outcomes: Approaches for Enhancing Access to Epinephrine. My name is Valerie Parker. I'm an assistant research director on the biomedical innovation team here at Duke-Margolis Institute for Health Policy. I'm excited to welcome both our virtual and in-person attendees to today's meeting, which is being convened by Duke-Margolis and our colleagues at the US Food and Drug Administration's Center for Drug Evaluation and Research. Today, we'll be discussing anaphylaxis, a severe, progressive, allergic reaction that can cause airway obstruction, shock, multiorgan failure, and ultimately death if not treated promptly and appropriately. Epinephrine is the only effective first-line treatment for anaphylaxis that is approved by the FDA, and therefore ensuring patients having access to epinephrine when they need it is critical to improving anaphylaxis outcomes. And that will be the focus for our meeting today. There are many different elements to ensuring access to epinephrine and many different barriers that might hinder a patient's ability to get epinephrine and use it to treat anaphylaxis if it occurs.

Numerous steps have been taken to address many of these barriers, including by many of the individuals and organizations who are joining us for today's meeting. And I'll leave it up to our incredible lineup of speakers to share much more on all of these points throughout the day. To start, I'll just review some important logistical information regarding the meeting. A few logistics before we dive into today's content. On the screen is a short note about our commitment to academic independence. You can find more on our policies on the links on this slide. Duke-Margolis is convening this workshop under cooperative agreement with the US Food and Drug Administration. The conversation today, while supported their cooperative agreement with FDA, is not a federal advisory committee. We will not be voting, making recommendations, or conducting other binding actions. Our goal today is to facilitate a balanced, nuanced discussion on how best to enhance access to epinephrine to in turn improve patient outcomes.

Attendees, both in-person and online, are encouraged to submit questions to the Slido Q&A function. Those will be passed along to the moderator. We want to ensure today's discussions are dynamic and responsive to the community gathered here today, so please don't hesitate to submit questions. And the QR code function will allow you to ... Will be included on the following slide and will be displayed again during discussions for your convenience. You can also access the Slido platform, submitting

questions by going to Slido.com and entering the code, EPI. E-P-I. If anyone joining us online has any technical difficulties, please feel free to reach out to our event staff using the email listed on the screen. And for those of you in-person, please feel free to find any Duke-Margolis staff member for any questions or concerns you may have. And then lastly, all meeting materials will be accessible on the Duke-Margolis website.

And currently, you can view the agenda, discussion guide with background information and a speaker bio sheet with information on all of our speakers, including any relevant disclosures for conflicts of interest for each of them. Please note that our event webpage also includes a link to the FDA's public docket associated with this meeting, and that docket will remain open to the public for comments until January 16th, 2026. So we encourage attendees to share their thoughts via written public comment. Shortly after this meeting, we'll also post a recording, transcript and the slides that are used today.

So we'll begin our event today with some remarks from FDA on the importance of this topic and the aims for this meeting. And our first session will consist of a couple of presentations and a moderated discussion on the current clinical guidelines and practices for diagnosing allergic diseases, as well as diagnosing and treating anaphylaxis. Then after a short break, our second session will include presentations from FDA on regulatory pathways for epinephrine products, both for prescription and non-prescription drug development. Then the panel discussion will consider how patients and caregivers might navigate the process of identifying allergic diseases and anaphylaxis and administering epinephrine when appropriate if epinephrine products were available without a prescription.

We'll then break for lunch and return for a public comment session in which a number of interested individuals will prevent brief remarks on treating anaphylaxis and enhancing epinephrine access. Of course, time limits the number of public comments we're able to hear live during today's meeting. So again, please remember that FDA's public comment docket is open for further comments. Our final two sessions in the afternoon will broaden the scope of it. The third session will consist of moderated discussion on current patient access to epinephrine and barriers to access. And then to conclude the day, we'll have a forward-looking discussion session on opportunities to enhance access to epinephrine, following this meeting, what we can all do to continue the work toward improving outcomes for patients at risk for anaphylaxis.

For this final session, we're really interested in hearing from you all on what concrete productive steps can be taken by this collective group of stakeholders to immediately advance access to epinephrine. Please do feel free to share those immediate next steps ideas at any time through the Slido platform. Now, without further ado, it's my pleasure to introduce our first speaker who will be joining us virtually, Dr. Mary Thanh Hai, the director of the Office of New Drugs at FDA. Mary, thanks so much for joining us today.

Mary Thanh Hai:

So good morning. I am truly honored to be given the opportunity to provide opening remarks for this very important workshop aimed at improving access to epinephrine to treat anaphylaxis. On behalf of the Office of New Drugs and the Center for Drug Evaluation and Research at FDA, I would like to thank everyone for joining us today in-person and online. I'm truly sorry that I'm unable to join you in person as I have several conflicting meetings today that require me to stay at the White Oak Campus. Before I go much further, I have to state that I have no conflicts of interest to disclose. So with that, now let me turn to the matter at hand. Anaphylaxis is a severe, rapidly progressive allergic reaction to allergens to which individuals are sensitized, and these allergens may include foods, drugs, and insect venom. Anaphylaxis can occur at any place, at any time, and can be fatal if not promptly treated with

epinephrine. In severe cases, failure to promptly treat anaphylaxis can lead to airway obstruction, shock, multiorgan failure, and death.

Despite being the only effective first-line treatment approved by the FDA, barriers may limit access to and the use of epinephrine. The focus of this meeting is to discuss barriers to epinephrine access and use, unique considerations regarding epinephrine drug development, and different regulatory and policy approaches that could help address potential barriers with epinephrine access and use. Today's meeting brings together a variety of academic experts, consumer advocates, and other stakeholders to provide a broad range of perspectives on these important issues to inform the public health efforts of the agency. We also hope that these discussions may spur industry to develop more products in this space. We encourage any potential sponsors wishing to develop therapies that address anaphylaxis to reach out to FDA for advice on the development programs. If you're unsure of the right FDA point of contact, you will have the opportunity today to hear from and meet the scientists at FDA who are directly in charge of reviewing applications for the treatment of anaphylaxis, including epinephrine.

These scientists are for the most part in the Office of Non-Prescription Drug Products and the Division of Pulmonary, Allergy, and Critical Care in the Office of New Drugs. I want to thank them and staff from Duke-Margolis Institute for Health Policy for organizing this workshop. Both the FDA and Duke-Margolis have identified speakers and panelists for today's meeting. Thank you to all of you for donating your time and expertise to provide your perspectives and to the members of the public who submitted requests to speak during the open public hearing. We look forward to hearing your input. We look forward to working with many of you to find solutions to improve access to epinephrine and effective treatment for anaphylaxis. And as a reminder, we welcome comments from the public. The public docket will remain open for 31 days after this meeting. Thank you again for this opportunity. I'll now turn the meeting over to the moderator. Thank you.

Paul Greenberger:

Thank you, Mary. I'm Dr. Paul Greenberger, Professor of Medicine, Emeritus in the Division of Allergy and Immunology at the Department of Medicine, Northwestern University Feinberg School of Medicine in Chicago. A pleasure to be here with you and to join with the expertise not only on our program, but in the audience and by Zoom for this very important subject matter. The first session, which is going to go until 10:30, is entitled Allergic Diseases, Anaphylaxis and Treatment of Anaphylaxis in the Community Setting. And we have some questions we're going to get to for discussion as well. But the first part has to do with two speakers, both experts and both contributing a great deal to our field. And I want to start with them. The first is Dr. Hugh Sampson, who is the Kurt Hirschhorn, Professor of Pediatrics in the Icahn School of Medicine at Mount Sinai. The second is Dr. Julie Wang, who's the Professor of Pediatrics in the Division of Allergy and Immunology at the same institution, Icahn School of Medicine at Mount Sinai.

I'm going to ask you to come up first, and we're going to talk about current ways to diagnose and what's published, what's accepted, and we're going to get to treatment as well.

Hugh Sampson:

Thank you very much, Paul. Good morning, everyone. I feel honored to be here. I actually started my career at Duke, so it's nice to see the Duke name here. So I was asked to talk about allergy diagnosis and management briefly to give people a little bit of background on what the allergist is going to face. And I will also bring up a couple of the other major causes of anaphylaxis that we need to deal with. I thought I would start off by just giving a little background. I stole, as you can see, from the Allergy and Asthma Network's webpage, but this just gives us a little bit of a sense on what the size of the problem is. As

most of you probably know, food allergy has become very common. It's estimated about 30 million Americans now have a food allergy, about 10% of adults, 6% of children.

And the fact that we need to consider here today is that almost half of these individuals have reported experiencing a severe allergic reaction or anaphylaxis. The other big area that I'm not going to deal with much in the way of diagnosis is bee sting allergy. And this is a similar situation where individuals are at high risk, and it is estimated about 72 deaths per year from insect sting allergy. And then another area that's really probably the largest is that of drug allergy. And this though is primarily an in hospital situation, and today we're going to be discussing more in the community. The other issue is related to latex allergy, which is not quite as common. So my objective today is to try to understand how the allergist goes about making the diagnosis of food allergy and some of the other, what I'll call preventable causes of anaphylaxis, as well as to understand what we do to manage these patients and how we can try to prevent the development of anaphylaxis.

So I just want to give you a little bit of a sense of what we see when a patient comes in complaining of some reaction, food allergy to a food. The first one, a 10-month-old vomits repetitively two hours after ingesting rice cereal. This is something called food protein-induced enterocolitis syndrome. It's a type of allergy, but this is not one that responds to epinephrine. It's not IgE-mediated. Probably one of the most common ones you'll see with adults, example, 42-year-old comes in complaining of abdominal pain, severe bloating, diarrhea after eating something like pizza or ice cream. And this is somebody with lactase deficiency, not an allergy. You know not to use epinephrine. Next, one that we see, I think more commonly in our allergy clinics, the 12-year-old who comes in with a history of anaphylaxis after ingesting a trail bar. And it turns out that there was a tree nut in there that this individual was not aware of, and this is something where you would definitely need emergency epinephrine.

Another scenario may be family members come in and complain that after ingesting tuna at a restaurant, developed generalized pruritus, facial erythema and vomiting. This is scombroid poisoning. This is not a food allergy, although it may appear to look like that. Another would be a three-year-old with atopic dermatitis who the mother notes has flares of eczema after ingesting egg. This is likely IgE mediated. In this case, it's not developing an anaphylaxis, but certainly could. Next, a 24-year-old who comes into the emergency room complaining they got steak stuck. They had a steak dinner, and now they've got this obstruction in their chest. This is not uncommon in something called eosinophilic esophagitis, another form of food allergy. Again, not one that's going to be responsive to epinephrine. And then the last is a hunter who comes in complaining about anaphylaxis four hours after ingesting steak. This is now the alpha-gal allergy, and this one is quite different than what we typically deal with in our pediatric population, at least to this time. And it is also responsive to epinephrine.

So how do we sort all these out? Basically, it requires a careful history. We then have to choose the appropriate tests, interpret those tests accurately. Once we make the diagnosis, it's important that we educate the patient on what the allergy is, how to avoid the allergen, we set up an emergency plan, and then today, happily, we can actually discuss some potential therapies, but I'll go into the diagnosis and management a little bit more thoroughly. So the first thing, and probably the most important thing is the history. And what we want to know is that obviously what the food is or what the situation was, and then the timing of that reaction. Did it occur immediately? Did it occur a couple hours later, four hours later, things like that? That's very important in helping us decide what we're looking at.

We want to know exactly what the symptoms were. Skin symptoms, things like urticaria, generalized flaring erythema, often associated with IgE-mediated allergy. Gut would be nausea, vomiting, abdominal cramping, diarrhea. Respiratory can be anything from the upper airway, some nasal congestion, rhinorrhea, sneezing, watery eyes, but they're troublesome as you get down into the lower airway with chest tightness and wheezing. And then also cardiovascular where you may actually see hypertension.

So we want to know exactly what the symptoms were, what the timing of that was. We then want to have an idea of what kind of food they actually ate. Was it raw? Was it cooked? Because especially in the younger population, we see children will tolerate things like baked egg and baked milk, but will not tolerate it in a less cooked form.

We also want to know if it's reproducible. If the patient has experienced that previously, similar symptoms, and that greatly increases the likelihood that this is in fact an allergy. And then we want to know how they treated it and what the outcome of that was. And today we know there are also many co-factors that can prompt individuals to have reactions such as exercise, fever, alcohol, certain medications like NSAID when they're taken in conjunction with a particular food. So when we do the history, the history really provides us with what we call pretest probability. It directs our allergy testing, and it gives us an idea of how likely it is that this individual would experience an IgE-mediated reaction. And the diagnostic test that we'll go over in a second are really just to support that diagnosis but if you have a test in isolation that does not indicate somebody has a specific allergy.

So when we look for IgE-mediated allergy, the most typical on first-line evaluation is the skin test. And this is basically just putting a small amount of the extract of the food on the skin, making a prick in the skin, and looking for the development of a small hive or what we call a wheal and flare at the site of the reaction. What we know is from work done by Richard Sporik in Australia related to the skin tests, and our more recent work with serum IgE levels is that the larger that wheal size or the higher the level of Ig to a particular food, the more likely it is that that individual actually does in fact have an Ig-mediated food allergy. But the thing that to bear in mind, as I said before, a test in isolation does not make the diagnosis. A negative test does not absolutely rule out somebody having a food allergy or a very high level does not absolutely indicate that somebody does have an Ig-immediate reaction. So there has to be context with the history.

This is just to give you an idea of some work done looking at serum IgE levels. This was to egg done a number of years ago. Basically what we were able to show that once you exceed a certain level that you have a 95% likelihood, excuse me, of reacting to a particular food, and the lower that level, the less likely it is that you would experience it. And over the years, other foods have been looked at and 95% predictive levels have been determined for those foods. Two things to remember, again, this in isolation does not make the diagnosis, and the level does not correlate with the severity of symptoms a patient is going to receive or experience if they have an accidental ingestion, which patients are frequently told, and also does not correlate with the amount of food they ingest or need to ingest in order to elicit that reaction.

So oftentimes, even with these tests, while we can make the diagnosis pretty accurately from this, in the majority of times, there are going to be times where it's not so clear, and that's when we go on to the oral food challenge, and that can be either what we call open or double-blinded. The double-blind is nobody knows what the patient's getting. They're giving successive doses to see whether or not the patient experiences symptoms. The open, which we do mostly in clinic, is just generally give the patient the food and look for symptoms. And on your left there are the different symptoms that we're looking for, those things that I just described with the skin, respiratory, gastrointestinal, cardiovascular. And certainly when we do these challenges, we're hoping we don't ever get to the cardiovascular, but that is always a possibility. So this is something that the allergist always struggles with, it's when do you consider adequate symptoms to make the diagnosis of food allergy?

We sometimes see very subjective symptoms. In our general clinics, if you get a series of what we would call subjective symptoms like tight throat, itchy mouth and itchy skin, maybe one hive here or there, that is not in itself diagnostic. However, if it's to a strange food that the patient never eats, do you push on to get more definitive symptoms? So in the clinical setting, we push less hard. In the clinical trials that

we do, they mostly demand that we do see objective symptoms. Now, once you make the correct diagnosis, then it's important that you sit down with a patient and explain to them how to avoid the food. And for most of my career, that's all I did was tell people how to stay away from a particular food.

We need to educate them how to recognize early symptoms of anaphylaxis, because we will give them treatment, I'll be going to a little bit, and then Julie will talk about it much more than I will, but we need to give them a plan what to do if they start to encounter some of these symptoms. The other thing we do typically with the young infants who are egg and milk allergic is we do recommend giving a challenge to baked milk or baked egg because we now know about 80% of these young infants with egg and milk allergy will actually tolerate it in its fake form, and that makes life a whole lot easier. And there is some evidence that it may accelerate development of full tolerance to egg.

We also may want to talk to them about forms of therapy, especially the very young infants, because some of the data now coming out suggests that the earlier we start, like in the first year or two of life, the more chance we have of actually putting them into a state of tolerance. And at the moment, we have the FDA-approved peanut powder for doing that treatment, although many allergists around the country are doing it with homemade brews. And then we also want to talk to the older patient now that we have omalizumab available. Especially those with multiple food allergies, we recommend that they start on omalizumab because we know that that increases their threshold and makes it less likely that they'll experience symptoms if they have an accidental ingestion. And I think one of the most encouraging things to me after being in this field for a long, long time is the fact that there are at least 25 different therapeutic approaches in the pipeline. So there really is a good chance that we're going to be able to do more effective therapies for this patient.

Now, the other thing when we talk about avoidance, we also need to educate the patients about potential cross-reactivity, and this is something that we see people having mistakes with. So for example, somebody who's cashew allergic is highly likely to react to pistachio, same thing with walnut and pecan. So you need to make sure that they're aware of these potential cross-reactivities. One of the most common things we see in very young infants with cow's milk allergy is somebody will say, "Well, go ahead and have goat's milk or go ahead and have sheep's milk." To somebody with cow's milk allergy, it's virtually identical and they will respond. So you need to make them aware of that. Also, in individuals with various pollen allergies in the Northeast, we have a lot of birch pollen allergy. We see a lot of what's called oral allergy syndrome or cross-reactivity between birch pollen and many of the fresh fruits and vegetables that will give itchy mouth and not typically systemic reactions.

Sort of the question today is then who do we advise go on to or to have epinephrine available in case of an accidental ingestion? And in those who are at high risk, we obviously go ahead and prescribe epinephrine for them, some form of self-administering epinephrine. And then what about the people at lower risk? Well, then the question is, what's high risk and what's low risk? And I think Julie will probably discuss that a little bit more. But basically in the area of food allergy, if they've had an anaphylactic reaction or they have the potential to have an anaphylactic reaction, we do recommend that they get epinephrine. What about this pollen allergy syndrome or oral allergy syndrome?

Those almost never go on to systemic reactions, but they can. So if you have somebody who actually had experienced more systemic reactions, you would then, in those cases, think about giving them a prescription for epinephrine. With insect sting, again, that's something if it's just a large local reaction, we don't typically give those individuals prescription for epinephrine, but if they've had a systemic reaction, we definitely do. Individuals with a latex allergy, we don't see that quite so much. With drug allergy, it really depends on their occupation, but in most cases we don't. I didn't mention exercise-induced anaphylaxis. There's also food-associated exercise-induced anaphylaxis. Those individuals do in fact get a prescription for epinephrine. There's also something called cold induced urticaria, individuals

who potentially could jump into a pool, get generalized urticaria to systemic reaction. So those individuals would also be given epinephrine. So then in summary, just to recap how we think about it, we start off with a detailed clinical history for informing our diagnostic workup, and then we do the appropriate workup and interpret the tests.

In talking about epinephrine, we're looking at solely IgE-mediated food allergies. Once we do make the appropriate diagnosis, we inform them on how to go ahead and when to use the epinephrine and how to use the epinephrine in order to prevent full-blown anaphylactic reaction with that.

I acknowledge Julie Wang, who's a professor at the Icahn School of Medicine who will talk more about management.

Julie Wang:

Thank you, Hugh. Again, thank you for being patient and joining this very informative session and also happy to be speaking, but so excited to hear from everybody else. So if my slides could be put up.

Hugh Sampson:

It advanced.

Julie Wang:

All right. So I'm giving an overview on anaphylaxis and I'll cover the definition of anaphylaxis, signs and symptoms, as well as management with self-administered epinephrine. So number one is recognizing anaphylaxis. And so this is a publication that came out earlier this calendar year. It is a consensus report covering the definition, overview, and clinical support tool. Obviously, there have been anaphylaxis definitions, varying versions from different organizations over time, but one of the challenges has been that these definitions just differ in various ways. And so having a unified definition would support clinical and research efforts. And so this consensus panel consisted of 46 members internationally, as well as representing multiple medical specialties, not just allergy/immunology, but emergency medicine, intensive care, role as primary care. And the outputs of this consensus document was supported or endorsed by a variety of medical organizations that you can see on your right that are not only American medical societies, but also across the world internationally, again, covering not just allergy/immunology, but emergency medicine, primary care, et cetera.

So this aims to point everybody toward the same definition and the same criteria so that we can be speaking about anaphylaxis in the same way. So the anaphylaxis is defined as a serious allergic reaction that can progress rapidly and may cause death. It may involve the skin/mucosa, respiratory, cardiovascular, and/or gastrointestinal symptoms. And life-threatening anaphylaxis is characterized by respiratory and/or cardiovascular involvement and may occur without skin or mucosal involvement. So that's a key statement, part of it, because standardly, most people think that I will know an allergic reaction is happening because I'll see something on the skin. But in fact, that's not always the case. And so this is an important point to convey to patients and caregivers. So this is a clinical support tool designed for healthcare professionals. So there are three situations in which we hope that anaphylaxis rises to the top of the differential.

So it may not guarantee that the patient is having anaphylaxis, but we need the clinician to be thinking about anaphylaxis if any one of these scenarios presents in a patient. Number one, their patient does not know of any allergen exposure or doesn't know that they have an allergy, yet there's a sudden onset of illness within minutes to several hours with skin symptoms and either respiratory or cardiovascular symptoms. Scenario two is if there's likely allergen exposure, in which case a sudden onset of two symptoms in two or more of the different organ systems should make anaphylaxis rise to the top of the

differential. And then scenario three is someone with known allergy, knows that they were exposed and they had a sudden onset of either respiratory or cardiovascular symptoms, in which case, again, anaphylaxis should be really high on the list of things to consider. In terms of the organ systems involved, anaphylaxis can affect pretty much any organ system.

And so as part of the clinical support tool, some key symptoms in each of the organ systems are listed and color coded here. So skin and mucosal symptoms are considered to be one system, and then respiratory, cardiovascular and GI are listed as well. Of note, infants may present with signs and symptoms that don't typically show up in older individuals. And so there's notation in several of these areas just to highlight that, especially for the healthcare professional who has not had extensive pediatric training. So as an example, under mucosal, an older individual may say that their mouth itches or that there's throat discomfort, but certainly an infant will not be able to, one, verbalize that, so they may present with licking their lips or sticking out their tongue. And so subtle symptoms like this should be red flag in someone's mind. Now, once anaphylaxis is considered a possibility or high up there, then epinephrine is the next thing that should be thought about.

And so this is a guidance document published by the Joint Task Force on-

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Julie Wang:

A guidance [inaudible 00:33:01] document published by the Joint Task Force on Allergy and Immunology. And the Joint Task Force in the Purple Logo consists of members designated from the two major allergy organizations within the US, the American Academy of Allergy, Asthma and Immunology, and then the American College of Allergy, Asthma and Immunology. And this joint task force publishes practice parameters that serves as a guidance for our field so that, again, there's a standard in terms of how we are diagnosing and managing allergic and immunologic disorders. So this is the most recent one covering anaphylaxis, and several of these points are listed in this guidance document. So epinephrine is first-line treatment of anaphylaxis. There are several beneficial effects of epinephrine, including vasoconstriction or increasing vascular smooth muscle contraction, increasing the heart rate, increasing myocardial contractility, as well as bronchodilation. So again, the key areas that make potentially anaphylaxis threatening, respiratory and cardiovascular will be very well addressed by epinephrine.

There is plenty of data to show that early use of epinephrine during severe allergic reactions can improve outcomes, and these outcomes include decreased risk for needing additional doses of epinephrine, decreased risk of biphasic reactions, and then reduced hospitalizations and fatalities. Now, severe adverse reactions to intramuscular epinephrine are very rare. And so this is, again, stated in the practice parameter. And the beneficial effects of early epinephrine use, coupled with a high safety profile, really points us to that meeting diagnostic criteria for anaphylaxis is not required before the use of epinephrine. And so the standard teaching for our patients is that if you are worried about a severe allergic reaction happening, you don't have to check every box and make sure that anaphylaxis is 100%. As soon as you're worried, go ahead and use your epinephrine.

Now, many people are very comfortable with antihistamines and even steroids in the setting of allergic reactions. However, neither of these medications should be used in place of epinephrine for anaphylaxis. And here, I reference two other anaphylaxis practice parameters that have guidance statements related to these medications. The 2015 anaphylaxis practice parameter states that antihistamines are considered second line. They're great for treating skin symptoms, do not do anything for respiratory or cardiovascular symptoms. Corticosteroids have no role in the acute management of anaphylaxis, and that is at least in part because of their delayed onset of action. The 2020 anaphylaxis

practice parameters has this statement suggesting against administering antihistamines and corticosteroids as interventions to prevent biphasic reaction. So if that's a consideration, again, these medications should not be used specifically for this reason.

So majority of anaphylaxis cases unfortunately do not happen in medical setting, and so we do have to prepare patients and their families to manage anaphylaxis on their own, or at least start the treatment. And so providing a written allergy and anaphylactic emergency plan is key to this education. So this is the allergy and anaphylaxis emergency plan provided by the American Academy of Pediatrics. There are other versions of emergency plans out there from different organizations, but the key elements across the different emergency plans are quite similar, but I'm going to focus on the AAP plan in this discussion. So the bulk of the plan focuses on the signs and symptoms of allergic reactions.

The important reminder, again, to emphasize to patients and families is that they don't have to meet specific criteria. If they are worried, they should not hesitate to give epinephrine, which is why the statement on top is circled in pink. But if they hopefully are educated to some degree, they're not reading this plan in the midst of an allergic reaction, but there are signs and symptoms listed at the top that would suggest a severe reaction is happening, in which case epinephrine should be given right away. And then because it's a spectrum, allergic reaction can range from mild to all the way to severe. This plan covers the spectrum of severity. And so that's why there is a box at the bottom that states mild allergic reactions. And in that setting, what you consider something like an antihistamine to start. But again, this is not stating that antihistamines would be appropriate for anaphylaxis itself.

At the bottom of the plan lists the doses of epinephrine. Again, one is an educational tool for patients and families that really epinephrine should be prominent in your mind and not any other medication. Also, the fact that there are multiple epinephrine delivery options currently available. This helps the family understand that there are different options, but also facilitates a primary care or an emergency urgent care provider to prescribe the correct dose for that child's age and weight. So up until very recent years, there has been a brief statement that has been said over and over again to really simplify the teaching of give epi, call 911. That was intended to make things simpler for patients, but that had some unintended consequences. And we've seen many cases, and also it's shown up in the research that the calling 911 part has posed a barrier to epinephrine use because some families interpret this as if I don't want to call 911, then I should not give epinephrine, which is not the message that was intended in first place, but unfortunately that became something that people thought about.

We've also gained information about how responsive anaphylaxis can be to epinephrine over time. There have also been cost-effective analyses, so there's a lot of data that has led to the reevaluation of this paradigm. And so now there is a question of when should you call EMS or call 911? It's not an automatic. So this is the statement in the current anaphylaxis practice parameters that states that immediate activation of EMS or calling 911 may not be required if the patient experiences prompt, complete, and durable response to treatment with epinephrine. Now that's supported by data showing that many or overwhelming majority of cases of anaphylaxis will resolve with one or two doses of epinephrine. So this was a systematic review of meta-analysis that included 36,000 anaphylaxis events, and you can see that more than 90% were treated with one dose of epinephrine, and then more than 97% improved with two doses of epinephrine.

This is a publication that came out earlier this year that was a retrospective cohort study looking at anaphylaxis cases within the US and one in Canada, again, showing similar data that more than 97% of cases are treated with one to two doses of epinephrine. The study further identified that there are certain predictors for the need for additional epinephrine, and these include severe respiratory symptoms or severe cardiovascular symptoms. So these would be important factors to consider when

counseling a patient as to whether or not they should seek additional medical attention after they've given epinephrine for their anaphylaxis.

So in summary, it's important to teach recognition of signs and symptoms of anaphylaxis and how and when to use epinephrine. Families should be provided with allergy and anaphylaxis emergency plans to guide management of allergic reactions in the community setting. And then home management of anaphylaxis may be an option for some patients in some scenarios, but this requires shared decision-making as well as considering what the signs and symptoms are for that specific [inaudible 00:41:50]. Thank you.

Paul Greenberger:

Thanks so much to Julie and her excellent presentation. Please come on up and I'm going to add two more panelists and then we're going to have a discussion because we have until 10:30, which is great. Brian Vickery and Sharma, come on up, thank you. Let's see. Brian, we have him... Okay, there you are. Good morning. Good morning. Brian Vickery with us remotely, professor of pediatrics, Marcus Professor of Pediatric Immunology and chief of the Division of Allergy Immunology at Emory University in the Children's Healthcare of Atlanta. Here in the room is Hemant Sharma, chief of the Division of Allergy and Neurology Children's National Hospital in Washington DC and Professor of Pediatrics at George Washington University of Medicine. Thank you so much. I'm going to ask for comments from Brian first, but I'm going to ask a question. I think this has to do with history taking and our understanding.

This has to do with the physical conditions with the allergen. So I'm going to ask Brian, I'm going to come back to Brian to talk about A, why is a scrambled egg different from an egg that might be in a muffin in terms of allergenic potential? Hemant, milk, why milk out of the refrigerator versus milk in a cake [inaudible 00:43:31] you to talk about peanuts when I get a bag of trail mix, like you mentioned, and what about other forms of peanut and the allergenic potential? So I think I would like to do that before we come back to Brian. But Brian, do you want to start on egg, please?

Brian Vickery:

Sure. Thanks, Paul. Good morning, everyone, and it's just such an honor to be a part of this distinguished panel. Thank you for having me. So with respect to egg, you heard Hugh mention this earlier, and actually the folks at Sinai have done most of the work here, so I hope I get this right. Hugh and Julie can correct me. It turns out it's really interesting. There's a lot of interesting chemistry when you bake. Most of the allergens in egg are in the egg white. There's about 20 proteins that are known to be allergenic. There's three dominant ones, but they're in the egg white. And when you mix egg white proteins in the liquid phase to bake with a starch, typically wheat, and this is what gluten is particularly good at, but any other starch will do, when you mix these ingredients together in the wet phase, the egg white proteins form very strong chemical bonds with the starch.

And then you put that mixture in the oven, and as it bakes, not only is it exposed to heat for 25 or 30 minutes, but what happens is the mixture expands, the gas and the baking powder expand the mixture and the muffin or cake or bread rises. And under those conditions of expansion, those strong chemical bonds do not yield. And so what happens is actually the proteins become physically disrupted. They become sort of shredded during baking. And what this does is it disrupts the protein sequence so that the areas of the protein where IgE might bind are destroyed. And that means that, as you heard from Hugh, 70, 80% of patients who might react to a lightly cooked egg scrambled on the stove top where this chemistry and interaction with the starch has not occurred are able to tolerate the baked form because of this change, which is partly related to heat, but really more related to this chemistry and what we call the matrix effect of mixing it with a starch and baking it.

Paul Greenberger:

Thank you. Hemant, milk?

Hemant Sharma:

Well, thank you also again for this opportunity to participate in this important session. I feel like I want to say ditto to much of what Brian said because there's a lot of similarity, and I also echo what Brian had mentioned about my esteemed colleagues here who did much of this work at Mount Sinai. And so for milk, it's very similar in that when you're mixing it into this matrix, the heat breaks down and denatures parts of the protein that might be where the IgE binds, but interestingly, it preserves parts of the protein that might help drive tolerance. And so much of the research that has been done in this area looking at using baked milk and baked egg as immunotherapy was done at Mount Sinai, and it's been shown that that actually is a way to help accelerate or speed up the process of resolution of milk and egg allergy is using the baked egg, the baked milk as a form of immunotherapy.

Paul Greenberger:

Thank you. Hugh, peanut, please.

Hugh Sampson:

Yeah. So excuse me, peanut's very different. And one of the questions that we've always had is why is peanut so allergenic? Now, as is just mentioned with the baked egg or with the egg in the milk, it's not only this matrix effect, but you do get heat denaturation of the protein. And for some reason, very young infants make predominantly antibodies to what we call conformational epitopes, or the protein structure has to be still somewhat intact. But when, as Brian mentioned, when you cook it with a matrix with the high heat, you change the shape and then the antibody is no longer recognized, but they will continue for a while to recognize the less heated form. With peanut, it seems to be different. And with peanut, the kids that have reactions tend to make the antibody right away to these, what we call linear epitopes. So it doesn't really matter that it's heated.

And in fact, when you dry roast a peanut, it actually makes it somewhat more allergenic. So it's very different from what we're dealing with with egg and milk, and then tree nuts are probably similar. The other thing that's somewhat disturbing to us as allergists is how little of this protein in peanut and tree nuts that it takes to actually activate a reaction. Typically, with milk and egg, it's a little more of a volume. So this is something that has puzzled us for quite a while.

Paul Greenberger:

Thank you so much. As I know all of us really care about helping our patients and advancing the science and development of whatever we can to products and information to help our patients and advance the science. But as we take our histories, I think it's real important to make sure our histories are very precise. I'm going to go back to Brian. We'd like you to share some thoughts on some of the subjects of this session, what you've heard so far and what you'd like to add, please.

Brian Vickery:

Well, thanks, Paul. I think Hugh and Julie really put on a masterclass in terms of how we identify patients, make the diagnosis, and then provide them with the guidance they need to both avoid or lessen the possibility of future reactions and then be prepared to act if that were to occur. I think one of the things that I would just additionally emphasize is that in case it wasn't clear, there's a lot of

uncertainty in this process. I think we know that many more people than are actually allergic worry about being allergic and that they commonly present with concerns about allergy that we're able to resolve through the careful process of taking a history using judicious testing and finally doing a lot of oral food challenges, as you heard from Hugh to clarify the diagnosis. And we practice in environments in academic referral centers where that's easy for us to do and we have the infrastructure and the support needed to guide patients through challenges.

And at our place, we do hundreds and hundreds of these each year, but in community settings, these kinds of environments are not always available. And so there are a lot of patients out there who may believe themselves to be allergic, may have had some testing performed, and we know that sometimes the testing can actually overestimate the likelihood of allergy. And so there's a key issue with really making sure that patients are referred and evaluated appropriately because there's a problem with, I'll say, overestimating the condition because of the fact that many people make IgE and IgE is easily detectable, but as you heard from Hugh, that doesn't make them allergic. They have to have a good supporting history, and if they don't and there's still some uncertainty about the diagnosis, they ought to have a food challenge so that we really understand what's going on, but those challenges are not widely available to everyone.

Paul Greenberger:

Could you comment roughly in Atlanta area within many allergists, how many are actually performing oral food challenges for children? Do you have any idea?

Brian Vickery:

Well, it's a good question. I don't have a percentage or a number to give you quantitatively off the top of my head, but I will tell you that there's been some literature about this and it's certainly a minority of allergists. I mean, we estimate that there's somewhere around 5,000 practicing allergists in the US. And as you heard from Julie, not all of them necessarily are trained in pediatrics during their residency. Allergists can come at this from internal medicine or pediatric backgrounds, and yet they might be asked to evaluate a 12 or 15-month-old infant who's just had their first presentation. We encourage and expect our training programs to give our fellows in training a lot of experience in doing food challenges, but actually this doesn't happen widely. And so a lot of folks get out into practice and just don't feel comfortable and don't have the setup in their office to feel like this is a service that they can offer. And so it's really at these specialized referral centers where a lot of this work happens.

Paul Greenberger:

Thank you. Hemant, would you like to add in your thoughts regarding the presentations and the information so far?

Hemant Sharma:

Sure. Thank you, Paul. I agree with what Brian had said that you and Julie did a beautiful job of presenting the background here. And I think as I was listening, first, a huge presentation, I think this point about history really being a predominant thing that we have to focus on when we're assessing these patients is so critical. And thankfully it seems to be happening less and less, but we try to get the word out to primary care physicians not to send panels of food testing. So sometimes patients will come in with a concern for an adverse reaction to a food and the initial provider might say, oh, let's just send a food panel. And then we as specialists end up getting referred patients who have positive results on these panels to sometimes dozens of foods, many of which they're already eating and tolerating. And

that really can pose a significant risk because then if they remove these foods from the diet, studies have shown sometimes that might actually increase the chance, depending on how long they've been avoiding it, of a reaction upon reintroduction.

So the history is really what guides us predominantly. In listening to Julie's presentation, the other thought that came to mind is that we really are tasked with trying to educate our patients and families with very complex information. No two patients with a given food allergy are the same, even for an individual patient, though two of their reactions may be the same. And so we are trying to educate them about patterns to look for, to really rely on their gut. If they feel like things are progressing, go ahead and use the epinephrine.

But that lack of an algorithm that we can continually follow each and every time can be very anxiety provoking, and also for us as allergy practitioners, requires a good amount of time. And sometimes with the state of our healthcare system, the amount of time that it takes to thoroughly educate patients, particularly when they initially are diagnosed with food allergy about how to manage future reactions, that really is a complex task and often not easily completed within 20 minutes or 30 minutes of an initial visit. So I think the education is key and relying back on the history, as both Hugh and Julie have mentioned.

Paul Greenberger:

Thank you. Hugh?

Hugh Sampson:

If I could just add one thing just to reinforce what's being said about the history and thinking about what you asked me with peanut, I mean, some of the nuance we have to deal with, for example, is again, in the Northeast, we have a lot of birch pollen allergy. There's a protein in birch pollen that cross reacts with a protein in peanut. So we're seeing more and more teenagers who inject peanut start getting an itchy mouth, itchy throat and think they have anaphylaxis, and then they report that and they'll be prescribed epinephrine. Well, as I mentioned, with this oral allergy syndrome or food pollen syndrome, you don't need epinephrine. And there would be a lot of individuals if they don't get the appropriate diagnosis and management plan would be out carrying epinephrine when it's not necessary.

Paul Greenberger:

Oh, go ahead.

Julie Wang:

And I'll add to the complexity of this whole figuring out whether an allergic reaction is happening, the symptoms of allergy show up for so many other reasons, especially for young children. And viral infections is something that we encounter all the time. So there's an illness going around and then suddenly the child has hives and they associate the last food that the child ate as, oh my goodness, my child has an allergy because they drank the milk and now they have hives. And so there's a lot of teaching that we have to do and the nuances gets very difficult to tease apart because people think hives equal allergy when it's a symptom that can show up in infection as well. And so there's a fine balance of we want people to be recognizing allergy and appropriately worried about allergies, but we don't want them to be worried every single time a child has a rash or hives. And so that's another element of the allergy.

Paul Greenberger:

I'm going to ask you, Julie, since it's one of my questions, if the child got acute hives within 10 to 15 minutes of consuming milk and the hives are on the chest and maybe on the back and maybe some on the arms and the face was red, would that be an indication for epinephrine in that setting and for that family?

Julie Wang:

So in a child who has known allergy, then I would say yes, because what I teach my patients is your job is not to make the label of anaphylaxis. Your job is to identify that something is going on in a child that's worrisome, and because epinephrine is safe, that's why I'm prescribing it to you so that you can treat your child and not have the symptoms escalates. So yeah, a lot of my teaching is not so much about anaphylaxis, the label, but about when are there worrisome signs and symptoms that would make me think a bad allergic reaction might be happening and when they should use epinephrine and leave the label to the doctor. That can happen after the child has gotten all better.

Paul Greenberger:

[inaudible 00:58:08] that, how would you confirm that allergy was milk?

Julie Wang:

Yeah. So what I will add to link it to my previous comments is once the acute situation is resolved, then questions have to be asked about, well, was this the first exposure to milk? What was going on with the child? Were they self-feeding and just spilled milk all over themselves? Were they naked or not naked? Because there can be a contact irritation or contact hive. So I've seen quite a number of cases where the family comes to me and says, well, the child drank milk, got a bunch of hives, and so now I'm here at the allergist. But what did not occur was that nobody asked them the child had been drinking milk based formula their entire life, that there happened to be another child in the home that was febrile at the same time, and so it was true, true, but not related.

Paul Greenberger:

What would you do? Any lab tests?

Julie Wang:

If the child gave a full history of having tolerated milk, then no. And this happens all the time where the family might've stopped giving milk, but if you ask just a few more questions, the child ate ice cream yesterday or they had some cheese and some pizza or a cheese sandwich or mac and cheese. So the family stopped the liquid milk, but they didn't stop any other form of milk and that's the easiest.

Paul Greenberger:

And if you find out that a week or two later milk caused hives again within 20 minutes of having milk, would you do any lab tests? As I said, not a severe reaction, but acute hives in 20 minutes after eating.

Julie Wang:

In a setting of they are still continuing to eat other forms of milk?

Paul Greenberger:

Yes.

Julie Wang:

Again, I would go through what happened, self-feeding, contact irritation, were there something unusual happening? Was there a residual viral infection, new viral infection if child's been at daycare or school? So we really talk through with the family and go through the pros and cons of testing. Now, there will be situations where the family comes back to me two weeks later and they understand the conversation, but they just cannot get over the fact that this happened again, in which case we might choose to selectively test only milk, but with a strong caveat of we have to see what the result is and tread very carefully. We're not going to remove things from the diet.

Paul Greenberger:

There's a lot of involvement and thinking power that the physicians and healthcare professionals are required to be prepared to deal with. And I want to say to the people listening in, if you have questions, please send them in. I better talk about allergens in the Midwest briefly, Hugh. I've seen many people with pollen [inaudible 01:01:00] syndrome. I did have a patient who had allergic rhinitis and successfully treated with allergen immunotherapy for tree grass ragweed and did fine and had completed for three years with epi. But she went into a supermarket one day and got her usual smoothie, same flavor that she always got, but she needed some energy. So she pointed behind the counter, "I need an energy booster," which was this yellow material sitting in there and a couple scoops went in to the smoothie. And then shortly thereafter, she had acute respiratory distress, breathing difficulties, acute hives, and ended up in the emergency room.

And this was not the normal and this led to a project I had a fellow work on with me that it turned out that in the energy booster it was bee pollen, and bee pollen, the bees collect at the feet, collect the pollen as they go around doing what they do, pollinating, and we were able to show on the laboratory side and with an expert at Greer Laboratories looking under the microscope, there was tree pollen, grass pollen, ragweed pollen, an [inaudible 01:02:15] which is a mold in the energy booster that was bee pollen. So the allergens were consumed and the fact that a person had received allergen immunotherapy had no protection against, not a life-threatening, but a mild significant reaction to the consumed foods.

There are allergens in a fit food. This was where there's a lot of thought that goes into this trying to figure it out. So from Midwest, we have ragweed, and that goes up into Canada as well. I know we have ragweed here, but there was tree pollen in glass and malts that she ate. So usually people can eat their allergen and not have symptoms or reactions. Any other comments from our panelists? I have a bunch of questions. Brian, back to you, any comments?

Brian Vickery:

No, I think one thing that I would emphasize about the discussion so far and the recognition and treatment of anaphylaxis is the importance of early detection and early treatment. So I have a lot of empathy for a family member in this case, could be a patient as they get older, but a family member who's the caregiver of a child just recently diagnosed with an allergy, and now they have kind of become inducted into a club that they might not have wanted to join, where they now are a first responder and they are required to learn the skills of becoming a first responder, as you've heard. And not only assessing what might be going on, making clinical decisions as a layperson in a moment's notice, kind of by definition an emergency, and then deciding what do I do now? Do I give a medicine? Which medicine do I give? Do I need to call EMS or drive to the hospital? Should I call the office? What's the best course of action?

And of course, this is also in the context where this is happening to a loved one, and so their emotions are involved. It can be a frightening event. It's a complex skill for a parent or caregiver to learn how to do, and then eventually they have to learn how to train other people to do it, like maybe a teacher or a grandparent, somebody else who's going to assume care for the child. So there's a lot of skills that have to be learned. And it's not so much how to use the device, the epinephrine devices are relatively straightforward in terms of how they work, but it's really more of when and under what circumstances. And you heard that from both Julie and Hugh, but this takes a lot of work.

And in general, what we really want to emphasize is that, kind of like Julie said, when you're concerned that the reaction is not going the right direction, if it's generalizing, if it's spreading, if it's more than a single simple symptom, go ahead and use epinephrine because epinephrine after all is a natural hormone, it's adrenaline, our bodies make it. There's not a toxic dose that could be used in the community, and the data suggests that the earlier in the reaction that...

PART 2 OF 10 ENDS [01:06:04]

Brian Vickery:

The data suggests that the earlier in the reaction that epinephrine is used, the better the outcome in general. So we want to train people to understand when they recognize a reaction is starting to spread or starting to generalize, to go ahead and use epinephrine, which is a safe intervention. But this is a challenging thing for parents to learn how to do it and it's very stressful. They kind of feel like they're on call 24/7 and never get a break. And so it takes a lot of work with them to make them feel comfortable in this setting.

Paul Greenberger:

I'm going to ask you, would you advise epinephrine if there are hives, let's say 10 or 20 minutes after ingestion of a potential allergenic food, hives on the chest, some on the arms and the face is red. Would that be epinephrine... a time to inject or would you wait?

Brian Vickery:

Well, so I mean, again, it's a little contextual. I think it depends on that patient's other previous reactions. Do they have a history of asthma and so on? In general, cutaneous only findings, just a few scattered hives or maybe a swollen lip-

Paul Greenberger:

Pardon on me. This is a lot of hives on the chest. The chest is covered with hives. There's some hives on the arm. The face is red.

Brian Vickery:

Yeah. I mean, so again, those would all be considered cutaneous only symptoms and it would not be inappropriate to take an antihistamine and see how it progresses. But I think the minute that something else happens in a situation like that, the minute the nose starts to run or they sneeze or they cough or they start to feel abdominal pain, again, that's a sign, okay, things are spreading. Go ahead and use epinephrine at that point.

Now, again, the other thing that we're doing is we're training folks to be able to make these decisions on their own. Even if they call our office, we're getting information secondhand. If they call the on call

physician, you're trying to walk them through this, this is happening. You're going to have a low threshold in general to recommend epinephrine because they may not even be aware of all that's going on.

And I think that, again, it's a safe thing to do. So we encourage having a low threshold to act.

Paul Greenberger:

Thank You. Julie, I'm calling on you next. Would you to do things differently and when could the second injection or using through the nose or the shot be given if it's needed?

Julie Wang:

So number one is whatever the patient is prescribed, that's what they should be using. But in terms of the bunch of hives, I agree with what Brian said, I'm just going to add that there are other conceptual factors that I would consider. So if it's a mother and their child and they're at home in a very familiar setting and they have access to a phone, that is very different than, let's say a teenager who's out in the park, a bunch of friends. That teen, I would say just use it because I don't know if they're underplaying, under reporting what their symptoms are, if they're going to delay things. They're not with a responsible adult who could watch them.

But in general, I try not to have too big of a conversation around should you use it, should you not use it if they're on the phone with me, because I don't want them to be worried about epinephrine because I feel like if I'm hedging on the phone so much, that gives some messaging of, I'm not saying yes right away, I must be worried about it. And so they should be worried about it. So I generally try to push it back on the family and say, "I gave you the emergency plan. I gave you this epinephrine so that you can use it whenever you think that you need to use it. I'm never going to say that you did the wrong thing when you use it. I will be very happy for you and clap for you if you do use it and we'll never question whether it should have or should not have been given."

Paul Greenberger:

And when my that second shot... How long should they wait if they say things are not going well here?

Julie Wang:

Yeah. So I'd say you give it, you got to let things go for a few minutes anyway. So about five minutes later you see how things are going. If your panic is rising or your child's panic is rising, fine, just give the second dose, call 9-1-1 and get this over with. You don't have to sit there struggling to make this decision and escalating your stress level. It's unnecessary to do so. But if things have gotten a lot better and the family's comfortable, I'm fine with them saying, "You know what? Hold on to that second dose." And then you know what to look for. It's on your emergency [inaudible 01:10:42].

Paul Greenberger:

And the literature typically says, "As early as five minutes." And do you tell patients that, five minutes?

Julie Wang:

Yeah, I say, "Obviously you're not going to stop clock it, but after you use it, you're going to put the device down, you're going to soothe your child, they got a medicine," and that's a few minutes already to just figure out what's going on.

Paul Greenberger:

I'm going to ask you, since you've worked on this, comorbidities such as asthma in children with severe reactions, could you comment on that comorbidity.

Hugh Sampson:

Yeah, I think that our level of concern for giving of epinephrine definitely increases as somebody has a comorbidity like bad asthma, especially if there's been a history that they had wheezing and a previous reaction. I think we would be much more likely to tell them to go ahead and get that second injection.

Paul Greenberger:

And your work in 2001, for those of you interested in very important papers, we want to mention that about fatal reactions and comorbidity of asthma.

Hugh Sampson:

Yeah, so it wasn't the most fun study we did, but we did look at fatal reactions and what seemed to be the situation in which somebody experienced the fatal reaction versus non-fatal. And what we did see, and I know that there are some people that still question it, that patients that do have asthma, especially if it's not well-controlled asthma, are at much higher likelihood to have a severe reaction and potentially fatal.

So one of the things we always really work with these parents, if their child does have asthma, is to make sure it's under the best control we can have it because they seem to be at less risk than somebody who's just not well-controlled. Even somebody who has milder reactions but is not well-controlled does seem to activate more of the respiratory symptoms when they have an accidental ingestion. So again, we're much more likely to have somebody use epinephrine if there're wheezing symptoms involved.

Paul Greenberger:

I had the opportunity after your study to work with the medical examiner's office in Chicago, did 25 deaths from anaphylaxis, unselected causes, where yours was on foods, and the median age was 59 years of age. And number of people, most of them had not used epinephrine or not received it. And ischemic heart disease was a comorbidity in that population, and that included bee stings. I looked up the paper again, a 91-year-old in a series that died from ice cream, apparently with peanuts. So that was one of the unfortunate case of ischemic heart disease is another comorbidity. We're going to talk about heart disease later on in the next session.

But [inaudible 01:13:46], do you want to add in anything to this about how you counsel patients and families and when to administer the epinephrine and when might you administer this shot, or have it inhaled through the nose?

Hemant Sharma:

Yeah, I mean, I think that a lot of the key points here we've discussed. One thing that I sometimes mention to patients is that the delayed use of epinephrine is what I worry about more than you using it. And I think we've said that in a variety of different ways here, but just trying to reassure patients that if you think that things are progressing, go ahead and use it. Don't wait, because we do know that that delay or the lack of use of it is really what is a much bigger risk than using it.

And in terms of the second dose, similarly, I think Julie's data that she presented about the fact that thankfully the majority interactions don't require a second dose, but if within five minutes things are not

headed in the right direction, things are not starting to resolve, or if they're getting worse, then going ahead and giving that second dose.

Paul Greenberger:

Thank you.

Hugh Sampson:

Well, if I could also say, I think one of the most important things going on right now, and I would encourage the investigators who are doing it, is this disconnect between using the EpiPen and going to the emergency room. I mean, that had always been the mantra. And I know I've had many patients, especially teenagers who decide not to use it because they don't want to go to the emergency room. They don't want to sit there for four to six hours. And so a lot of the ones that I've seen where they've had bad reactions, it's just they didn't want to go. So I think that's important. And I know that Tim Dribin maybe talk a little bit more about some of the studies he's been doing, but it's really necessary to try to make people understand that it's not an absolute. And don't hesitate to use the Epi just because you don't want to go to the emergency room because I find that as big a problem as just being afraid to use it.

Paul Greenberger:

Yeah. Well, I had that with people with idiopathic anaphylaxis or was told, "I was going to have to pay a $1,000 copay if I go to the ER, so I'm not leaving work." I had to encourage them to use the Epi to try to stop their reactions as soon as possible.

I'm going to turn it into Ryan... Or I'm sorry. Brian, since you advocate a lot from the payer perspective, one of our questions is, how do you use our therapies to fit into coverage, reimbursement, and do we need additional evidence to get more coverage from insurance plans?

Brian Vickery:

Well, I mean, we haven't talked a lot about barriers. I mean, we've talked a little bit about barriers to acting in the moment and how we educate folks to respond in the acute situation, but we haven't talked much about access to the medicine in the first place and that these devices for some folks are really quite cost prohibitive. Others, not so much, but it depends a lot on the plan. We have a few devices available to folks, not nearly as many in the US as there are in other places like Europe where there are many more forms of epinephrine available. And the way that payers tier the drugs, they may or may not be the preferred option that the patient or family is used to, those tiers change all the time. And for some folks, the cost structure and out of-pocket price for an epinephrine device, which they absolutely need, can be a substantial cost to them.

And so I think that we do have a lot of work to do to think about how we can address some of the barriers that ensures that patients have access to the treatment they need because after all, all these instructions that we give about freely using epinephrine early in the reaction, none of that matters if you don't have it with you at the time, or if you're reluctant to use it because if you do, it's going to be $500 to refill it. So having access to the medicine is a key point that we haven't covered much, and the payers have a lot to do with that.

Paul Greenberger:

Any other panelists want to comment on that, on getting payers involved or experiences or advice?

Hemant Sharma:

Yeah, I agree entirely with what Brian was just mentioning. I think part of what I hear sometimes from patients is, "Well, I haven't needed to use this in five years, and they expire after a year, Dr. Sharma. So do I really need to spend all this money every year to keep refilling these devices that my child hasn't needed over five years?" And we of course say yes. But then we try to understand, well, what are those barriers? And it really can vary quite a bit from family to family. I think this brings up the bigger notion of health equity within food allergy management and what are those barriers that families may be facing either related to lack of insurance coverage, lack of adequate coverage, the amount of their copay. Prior authorization, which sometimes can be a barrier where we're trying to get devices prescribed and depending on the insurance carrier, they say, "No, not that one, another one." And then if you prescribe another one, then it requires a prior authorization that you have to fill out. And then sometimes they still may not approve it fully based on the prior authorization.

So I think that the barriers that families face financially as it relates to getting epinephrine into their hands sometimes is a quite formidable barrier. And we as healthcare professionals sometimes also face barriers trying to get that medicine into their hands. It's not as simple as just clicking to send the prescription electronically to the pharmacy for many of our patients. At Children's, we have a very diverse patient population, a significant proportion of our patients are publicly insured, and depending on what specific plan they have, we have to work to figure out which device is specifically going to get covered. And that back and forth can sometimes result in them not necessarily getting the medication immediately. So I just echo everything that Brian said about access here.

Paul Greenberger:

Go ahead, Julie, because I think we should make a list, so to speak, of stakeholders that we could invite to a meeting, for example, who would be at the table to improve access and outcome for the population.

Julie Wang:

Yeah, I wanted to add that it's not purely the dollar amount that is a barrier in terms of the access. This back and forth phone calling requires a level of health literacy and perseverance and time and effort that is not necessarily uniform across the population. And so I have had patients show up at the pharmacy, it's not there, and that's where the ball gets dropped, and we don't always know about it. And so I think access at the payer level is not just the dollar amount, but also which ones are covered. And also, a couple years ago there were shortages and sending patients to pharmacies that were so far away from them. That's another, transportation issue. So there are so many elements that are clumped together under this access payer problem.

Paul Greenberger:

I can see our people from being involved from government, from insurance and different insurances, being as government, Medicaid, Medicare, insurance companies, labor organizations, professional societies. What are the thoughts about stakeholders that we need to bring together to try to really improve access? People in the room? And they've got something else. Or online? I mean, I'm thinking we want to improve access, that takes a lot of people, a lot of organizations that would have to come together. Hugh?

Hugh Sampson:

No, I was just going to say, I think the other person that needs to be at the table are the people that make the drugs. Certainly one of the big differences we see, I mean, we even-

Paul Greenberger:

[inaudible 01:23:02] my part. I apologize. Sorry.

Hugh Sampson:

I mean, number one, we see people that get it from other countries because it's a lot cheaper. Why is it like that? I mean, I remember the days when some of these auto-injectors were well below a third of what we pay now for them. So I think that has to be part of the discussion. I realize there's expenses and all that, but I think that has to be considered.

Paul Greenberger:

Yes. All right. Thank you for that. So we certainly need stakeholders involved and there are a lot of us involved with expertise and the development of the new products. I'm glad you pointed out that a lot of them are in the works and we wish success for all of them.

How does treatment vary if there's a lot of anxiety in the room? Hey, Marc, do you want to talk about that? This is the stress. The relatives with allergies, let's say to foods, somebody else had a reaction to penicillin with a lot of history of allergy in the family history, and now the child has seemed to be a compatible history and workup for food allergy. How does that play into what you advise?

Hemant Sharma:

Yeah, I think the stress associated with food allergy is multifold. We'll hear a little bit later from my colleague, Linda Herbert, who's one of the leaders investigating the psychosocial impact with food allergy. And I think as we initially diagnose a patient with food allergy, if there already is a family history, then that level of anxiety is already somewhat heightened, particularly if they've experienced severe reactions in the past. The word that comes to mind often is worry and fear. And so although thankfully reactions may not happen incredibly frequently in patients who have food allergy or other forms of IgE-mediated allergy, the worry about it happening, the what ifs really predominates much of day-to-day living. And if it's food allergy that we're talking about, everywhere you go, for the most part, there could be potential exposure to food, whether we're talking about schools, camps, public places. And so that definitely predominates much of what the day-to-day experience is. It's this worry of could there be an exposure and if there is, what then might happen.

And so it is an incredibly stressful condition to live with. And the epinephrine, I think sometimes layers on top of that. One of the things that we kind of touched on is things that could look like allergic reactions, but may not be. And I've definitely had patients where either in the setting of an oral food challenge or in the community with a reaction, we deduced that maybe it was more anxiety or maybe it was more of a panic attack that occurred after the possible exposure to the allergen. And in many ways, those things can be very difficult to distinguish from a true allergic reaction. You can have changes in breathing. With a panic attack, breathing can be very rapid. You wouldn't necessarily have wheezing. There can be complaints of GI discomfort associated with that as well. So often the psychosocial impact of food allergy, we need to take into account not only in the day-to-day life and living with food allergy, but also in the moment of reactions, trying to decipher could some of this be anxiety versus a progression physiologically?

Paul Greenberger:

And do you try to focus on a go-to person in the room, the caregiver? How do you deal with that? Who's really going to say epinephrine is now needed?

Hemant Sharma:

Yeah. I think a lot of it boils down to where we are developmentally with the given patient. So obviously if it's an infant, we're going to be focusing more on the caregiver. However, as our patients age into adolescence, preadolescence, we really wanted to make sure that they're involved in a lot of this education as well so that they feel empowered to self-manage their food allergy, to know what to do in the case of reactions. And so developmentally, there are some differences in terms of the education.

Paul Greenberger:

Thank you. You were going to add?

Hugh Sampson:

Well, I think one of the toughest things we've had to deal with is how to make sure patients appreciate the fact that they need to treat a reaction, but not to overtly scare them. And I think one of the problems, we may have overly scared a lot of patients. And their colleague in the UK did a study looking at likelihood of fatality from different things. And in the US, anaphylaxis to food is not the first problem for kids. Actually, gunshot is a higher amount. So I think one of the things we have to do is somehow be able to educate them on the necessity without scaring them.

And another factor is, it's also been shown that in a patient who's highly anxious having a reaction, they tend to have a worse reaction. So the anxiety actually plays into aggravating the severity of the symptoms. So this is an area and Linda's done a lot of really good work in this area, anxious to hear her solutions.

Paul Greenberger:

It's just about 10:30, so we can call this session to a close. We're going to take a break for 15 minutes. And feel free to continue the conversations with our faculty as well, but we'll be back in 15 minutes. Thank you, [inaudible 01:29:01].

Thomas Roades:

I'm Thomas Roades, I'm a policy research associate here at the Duke-Margolis Institute for Health Policy, and I will be moderating our next session today. I'm honored to have the opportunity to be a part of this event, especially as I'm a person living with severe food allergies. And my own life was saved by epinephrine when I was just a few years old, when my parents unexpectedly discovered that I had food allergies as the case for so many children and parents. So it's really a pleasure to be here alongside so many people who are doing excellent work to help patients like myself.

In our initial session just now, we heard a fantastic discussion on clinical practice related to the diagnosis and treatment of allergic diseases and anaphylaxis, including the use of epinephrine as the frontline treatments, as we heard. In this next session, we'll start with a presentation on how epinephrine has been regulated historically and how it is currently regulated by the FDA.

And then our second presentation will cover regulatory pathways for non-prescription products and the requirements for a product to receive that designation. Then in the moderated discussion portion, we will dig into the details of some considerations around potential non-prescription access to epinephrine,

thinking about how patients and caregivers would try to navigate diagnosis and treatment of allergic diseases and anaphylaxis without the counsel of a healthcare provider.

So we'll start with two presentations from FDA, as I said, and then the panel discussion. So I'll introduce our presenters first. We will start with the presentation from Miya Paterniti, the Clinical Team Leader in the Division of Pulmonology, Allergy, and Clinical Care at FDA's Center for Drug Evaluation and Research. And then right after that, we will have a virtual presentation from Karen Murray, the Acting Director of the Office of Non-Prescription Drugs and FDA's Center for Drug Evaluation and Research.

Miya, please come on up and start us off.

Miya Paterniti:

Thank you so much. All right. Down a little bit. All right, good morning. My name is Dr. Miya Paterniti, and as was stated, I'm one of the clinical team leaders in the Division of Pulmonology, Allergy and Critical Care at the FDA. I would also like to recognize my colleague, Dr. Jennifer Land, who is a major contributor to epinephrine [inaudible 01:31:19] product. I'm pleased to have the opportunity to open session two of today's workshop, and it is my privilege to present on FDA's regulatory framework for epinephrine products and the treatment of anaphylaxis, which are currently available via prescription. The presentation will provide essential regulatory context for our subsequent discussions.

Okay. So my presentation today will cover several key areas. The first is I'll provide some historical context for epinephrine regulation, then discuss the approval pathway for epinephrine auto-injectors, as well as labeled risks of epinephrine. I'll then examine the human factor considerations that are critical for emergency use devices, review chemistry and manufacturing challenges unique to epinephrine, explore alternative routes of administration, and conclude with key takeaways.

To establish the proper regulatory context, it is essential to understand epinephrine's unique historical position within FDA's regulatory framework. Epinephrine has a remarkably long history in medicine and in 1901, Parke Davis & Company first marketed adrenaline, and this predated the major federal drug regulation. Consequently, epinephrine was available as a marketed and unapproved product for many decades before our modern regulatory framework was established.

The evolution of auto-injector technology represents an advancement in emergency epinephrine delivery system. During the 1970s, Sheldon Kaplan and his group at Survival Technologies developed an auto-injector device that was initially made for medical and military use and was then moved into auto-injectors, and this was adapted for epinephrine administration. This resulted in the first FDA-approved epinephrine auto-injector, the EpiPen, which fundamentally transformed the therapeutic approach to emergency medicine anaphylaxis treatment in the community setting.

Here's the current regulatory landscape, and it encompasses a comprehensive portfolio of approved prescription epinephrine injection products across multiple delivery platforms. Within the auto-injector category, we have EpiPen and EpiPen Jr. Those were approved in 1987, followed by Adrenaclick in 2009 and Auvi-Q in 2012. Generic epinephrine auto-inductors were approved in 2018, and we have one prefilled syringe, Symjepi, that received approval in 2017. We also have vial-syringe products, Adrenalin and others that are used in the medical setting, and these received approval in 2012. Dosing is weight-based, as you can see, across products to allow for dosing in pediatric patients [inaudible 01:34:20] 7.5 kilograms in the community setting.

The regulatory approval pathway for epinephrine auto-injectors reflect a scientifically rigorous yet pragmatic approach to emergency medicine regulation. The established dose and injection route of administration are substantiated by more than 100 years of documented clinical use and peer-reviewed

literature. Epinephrine is universally recognized as the standard of care for anaphylaxis, as was mentioned [inaudible 01:34:52] this morning, with well-established efficacy and safety profiles.

Given that these products represent combination drug device products, FDA's regulatory review encompasses comprehensive device performance evaluation requiring 5-9s for reliability, representing an exceptionally stringent standard, in addition to rigorous product quality assessment, manufacturing validation, and human factors evaluation. Notably, pharmacokinetic data is not required for approval and clinical efficacy studies to support approval have not been conducted for approved epinephrine products. I will provide additional details regarding product quality and human factor presentations later in this presentation, and also to clarify that the statements made for this slide in terms of the PK data and is specific to injection products.

As a result of the approved process of epinephrine injection product, epinephrine is labeled for several risks. Epinephrine risks are generally well-established and are based on clinical use and literature. Risks of epinephrine use include various cardiovascular effects listed here, and these include angina, various arrhythmias, including potential fatal ventricular fibrillation, cerebral hemorrhage, and others. Patients with underlying cardiovascular disease are at higher risk for these adverse reactions. Epinephrine can also cause transient hyperglycemia and sweating as well as neurologic adverse reactions such as disorientation, psychomotor agitation, and others. Psychiatric adverse events can also occur including anxiety, apprehensiveness, and restlessness. Finally, respiratory difficulties make paradoxically occur with epinephrine administration.

Next, we will discuss one of the critical aspects of epinephrine product regulation, which is human factor consideration. Human factors, also known as ergonomics, is the scientific discipline concerned with understanding interaction between humans and other system elements. In this definition, systems represent the physical, cognitive, and organizational artifacts that people interact with. For drug products, this means designing products that optimize human wellbeing and overall system performance. And during the development and design of a drug product's labeling and packaging, it is important to consider the intended use, for example, emergency use, the environment of use, and the product interface.

Based on the product's risk analysis, we may recommend that companies submit human factor studies to assess actual use of the product and collect data from representative participants in a simulated real world assessment. These studies help to determine whether users can safely and correctly perform tasks associated with the use of the product, characterize risk and develop mitigation strategies. The studies are generally small in size and shortened duration compared to clinical studies, and notably human factor considerations for novel routes of administration of epinephrine may introduce new challenges.

We shall now examine the unique chemistry and manufacturing challenges with epinephrine products.

Epinephrine presents significant formulation challenges as it readily oxidizes when exposed to air, light and temperature. This causes changes resulting in multiple degradants, which must be monitored for safety. Acidic conditions converts the L-active form of epinephrine into the inactive D-form, reducing effectiveness. Without proper formulation and storage, the medication may contain too much inactive form or harmful impurity to be reliably effective in an emergency situation.

Given these stability challenges, manufacturers must provide extensive stability testing to demonstrate that their product maintains strength, product quality, and purity throughout their shelf life.

PART 3 OF 10 ENDS [01:39:04]

Miya Paterniti:

... maintain strength, product quality, impurity throughout their shelf life. FDA examines multiple parameters, including epinephrine concentration, impurity levels, degradation products, and antioxidant contents. Testing must account for various storage conditions that affect medication stability and FDA sets conservative expiration dates based on these rigorous testing standards to ensure both efficacy and safety. To address epinephrine's inherent instability and solution, several development strategies can be explored. These include investigating new routes of administration, such as nasal or sublingual delivery that may not require solution in formulation, developing dry formulations, employing product strategy, using complex agents to reduce degradation susceptibility, exploring non-sulfide NF and using excipients with low levels of oxygen and metal ion.

Given these challenges with injection products, there's significant interest in alternative routes of administration of [inaudible 01:40:07]. Alternative routes being explored include intranasal, sublingual and inhaled. These routes offer potential advantages such as in patient compliance, earlier administration and higher carriage rates since these may be less intimidating than injections. However, they also have limitations, including local adverse events, diminished depot effect compared to intramuscular injection, potential impacts of mucosal abnormalities on absorption, and challenges with administration during anaphylaxis, particularly for effort dependent routes. In addition to human factors and chemistry manufacturing controls that are applied to all epinephrine products, a regulatory review for alternative routes focuses on establishing efficacy based on pharmacokinetics that are greater than or equal to approved injection products, with supportive hemodynamic, pharmacodynamics, including heart rate, systolic blood pressure, and diastolic blood pressure. Systemic safety is assessed based on pharmacokinetic bracketing between approved injection products, and local safety is evaluated based on adverse events reported during the development program.

Studies are performed in both healthy volunteers and allergic patients with local allergic reactions and clinical efficacy studies are not required. This approach was discussed at the FDA Pulmonary Allergy Advisory Committee in May of 2023. Our regulatory review of alternative routes of epinephrine faces several significant challenges. Since approval of epinephrine injection products is based on efficacy and safety from over 100 years of use, we have limited pharmacokinetic and pharmacodynamic data. And most studies are in healthy volunteers rather than patients experiencing anaphylaxis. We also lack dose ranging studies so the optimal dose during actual anaphylaxis is not definitively established. In addition, the pharmacokinetics of epinephrine injection products is highly variable as explained in detail on the next slide. This is potentially due to the impact of needle length on drug delivery, and how different devices like autoinjectors compare to a manual syringe system can affect delivery through factors like injection force and angle.

Here, you can see the pharmacokinetic profile for autoinjectors. The example given here is EpiPen and manual syringe product such as adrenaline. [inaudible 01:42:47] is on the X axis and epinephrine concentration is on the Y axis. There is a large degree of variability across product in terms of between the autoinjector and the manual syringe product. Epinephrine autoinjectors typically demonstrate early time to maximum concentration and higher peak concentrations. This is possibly related to the force of this and speed of administration with autoinjectors. Manual syringe administration on the other hand shows a later time to peak and lower peak concentrations compared to autoinjectors. [inaudible 01:43:23] absorption patterns have also been reported adding to the complexity of predicting response. There's also a large degree of variability within product, so you can see that there's multiple. If you look just at EpiPen or just at adrenaline, there is variability within those products. And this is likely due to the high degree of intra and inter subject variability.

Despite these challenges, the current regulatory landscape now includes a recently approved epinephrine nasal spray listed below in the bracket in red. In conclusion, I'd like to summarize the key regulatory points that we've covered in terms of FDA's framework for epinephrine product. First,

epinephrine's unique regulatory status stems from the fact that it predates modern drug regulation, efficacy and safety established through more than 100 years of clinical use and extensive literature rather than contemporary clinical studies. Second, for epinephrine injection product, FDA approval focuses on three clinical areas, human factor studies, device reliability testing, chemistry manufacturing control data to ensure safe and effective use. Finally, we've approved an alternative delivery route, epinephrine nasal spray, which was approved using pharmacokinetic bridging with supportive pharmacodynamic data compared to established epinephrine injection products. This regulatory framework establishes the foundation for evaluating epinephrine products and will serve as essential context as we move forward with today's workshop discussion.

As we continue to see innovation in this space, FDA remains committed to facilitating access to safe and effective epinephrine products while maintaining appropriate regulatory standards. Thank you for your attention. I look forward to the productive dialogue ahead.

Thomas Roades:

Thank you very much, Miya. And I'll just pop up here for one moment to introduce Karen Murray. Again, the acting director of the Office of Non-Prescription Drugs at FDA. We have Karen on the line here and ready to join us.

Karen Murry:

All right, thank you. And how's my audio?

Thomas Roades:

Very good.

Karen Murry:

Okay, great. So hello, I'm Karen Murry, and I'm acting director of the Office of Non-Prescription Drugs at FDA. My apologies that I could not attend in person. I also have a child with severe food allergies, so this is an area that's close to my heart. So you've just heard Dr. Paterniti's excellent presentation on prescription epinephrine and its regulation. And now I'll give an overview of non-prescription drug regulation, including some considerations around a possible future non-prescription epinephrine product. Next slide, please. So when is a drug considered non-prescription? Well, before 1951, prescription and non-prescription drugs didn't really exist as separate classes. Doctors prescribed most drugs, but in 1951, the Durham-Humphrey Amendment passed. This established two drug classes, Rx Legend, or prescription drugs, were those that required practitioner supervision because of "toxicity or potentiality for harmful effect or method of use." Everything else is non-prescription, commonly referred to as over-the-counter or OTC.

In the United States, we have only two classes of drugs, prescription and non-prescription. Note that the US does not have a third class of behind-the-counter or pharmacist dispensed drugs. Next slide, please. So what are the general characteristics of a non-prescription drug product? The drug has to have a good safety margin, meaning that there is a wide distance between the dose at which the desired therapeutic effect occurs and the dose at which toxicity or adverse effects occur, so that the benefits of non-prescription availability outweigh the risks. The consumer has to be able to self-diagnose, self-treat, and self-manage the condition being treated. The drug needs to have a low potential for misuse and abuse. The drug cannot require a healthcare practitioner for safe and appropriate use, and labeling is key. It has to enable consumers to self-diagnose, correctly, self-select to purchase, use properly, and to know when

to stop using or talk to a healthcare practitioner. Often, consumer studies are needed to show that the labeling works for these requirements. Next slide, please.

So here's a figure of drug development pathways. On this slide, moving from the top down, you see we're talking about human drugs, then prescription drugs on the left, and to the right, non-prescription drugs. I want to emphasize that it's still important to consider prescription drug approaches to expanding epinephrine availability. Now, within the non-prescription drug class, there are some subtypes. There's a broad division into two types, application products, which require an application for approval prior to marketing and monograph products, which I won't go into today because if a sponsor were to bring epinephrine forward, they would do so under an application and not the monograph. Now, within that application group, there are three possibilities. You can actually bring a product to market directly as non-prescription without it ever having been prescription. That likely wouldn't apply to epinephrine. Epinephrine would come in under the prescription to non-prescription switch pathway, which you may have heard referred to as RX-OTC switch.

And there might be a couple of ways that could be done. The traditional way using labeling alone to support safe and effective use, or if labeling alone isn't adequate, one might be able to use a new way, which can add something to labeling to support safe use. That way is called additional condition for non-prescription use, abbreviated ACNU, and I'll talk more about that later. Next slide, please.

So you've heard we'd be talking about a prescription to non-prescription switch program. Well, how does such a development program work? This is general information, not specific to epinephrine. Usually, and in the case of epinephrine, the program would rely in part on the safety and efficacy information that we already have for the prescription product. And speaking generally and not specifically about epinephrine, sometimes new clinical studies are required. Typical examples are when proposing a new indication or a new patient population. Sponsors need to identify the key elements of the prescription label and translate them into consumer-friendly terms. This is often hard. Literacy in the US is low, with an average reading level somewhere between fifth and eighth grade, and health literacy is even lower. Consumer studies, which I'll cover briefly later, are needed to evaluate the suitability of the product for non-prescription use. As I mentioned above, the issues that need to be addressed in the development program are identified from the prescription labeling and also from data on clinical use.

Next slide, please. A major task of the sponsor is to develop a drug flex label or DFL. Non-prescription drug products must comply with the code of federal regulations, including meeting DFL requirements. On the right side of this slide is an example DFL. You're all probably quite familiar with the DFL from when you have purchased and used non-prescription drugs. It's intended to ensure consumers can self-select correctly, meaning that they correctly determine that this non-prescription product is right for them in their personal medical situation. The DFL also needs to ensure that the consumer uses the drug effectively and safely without any assistance from a healthcare professional. You'll recognize the strong linking of the DFL function with the statutory definition of a non-prescription drug that I mentioned earlier. Next slide, please.

That small DFL space contrasts sharply with the label for a prescription drug, which is called the full prescribing information or FPI. Here's an example. Obviously you can't read it. I'm just illustrating how long it is. As you can see, it has multiple pages and includes lots of text and graphics. This is for doctors, not for consumers. You can see how if you switch a drug from prescription to non-prescription, that it can be pretty tricky to get everything you need to know onto that little drug fix label that you saw in the previous slide. And this is just an example label, 15 pages long for a non-epinephrine product. Prescription epinephrine products have even longer prescribing information. Next slide, please.

So let's say a company has developed what they believe is a good drug fix label. What next? Generally, one or more consumer studies are needed. Now, again, this slide is about consumer behavior studies in

general and not specifically about what might be needed for epinephrine. At the top, label comprehension studies are almost always needed. No matter how carefully one writes a DFL, people often don't understand key aspects of it. The label is tested in an iterative fashion, getting better and better comprehension until there's good evidence that study participants are understanding the label and thus that consumers are also likely to understand it. Sometimes self-selection studies are needed. This is where beyond just comprehending what the label says, a study subject considers their own personal medical situation. For example, if they're taking interacting drugs or have a condition that might make it not safe for them personally to use the non-prescription drug, the participant makes a decision about whether the drug would be appropriate or not appropriate for them as an individual.

In a few cases, concerns about the likelihood of safe use in the non-prescription setting lead to the need for what's called an actual use study, where study subjects actually purchase the product and use it in a clinical trial setting with data collected on correct use and safety. And finally, there are sometimes human factor studies, usually when the drug is administered with a device where study subjects demonstrate that they perform key tasks correctly. You heard about the use of human factor studies in prescription development programs earlier. Next slide, please.

One thing I like to mention is that while we generally think about non-prescription drugs being tablets or capsules or topical formulations, any approved dosage formulation is a possible switch candidate within reason. The sponsor needs to provide adequate data to show that consumers can correctly administer the drug using the directions. Sometimes this means there is a need to develop and test a user-friendly format for the labeling and packaging to make safe and effective use more likely for the particular dosage form. Next slide, please. So the paradigm I've been covering is about how a development program would typically go prior to submission of an application for switch from prescription to non-prescription. And we do have quite a few non-prescription drugs that came to market this way, and they are helping consumers relieve symptoms of many everyday conditions across many therapeutic areas. However, the low-hanging fruit, as we say, is pretty much gone for straightforward switch candidates that can make it over the finish line using labeling alone.

And until recently, existing regulations made it difficult for FDA to consider means other than labeling to ensure safe and effective use. I want to give an example of a tough program for which FDA took a creative approach using labeling alone. And after that, I want to talk about a new option for non-prescription development that recently became possible. Next slide, please. Many of you are likely familiar with non-prescription naloxone. After FDA approved it, opioid overdose deaths declined dramatically after increasing year after year for many years. Naloxone wasn't low-hanging fruit. It was hard. It's administered in an emergency situation often by a bystander who may never have used naloxone before or even read how to use it, and the drug had many other challenging aspects.

However, we got there with labeling alone, the traditional path. Our ONPD team worked with experts in modern techniques for visual communication, community harm reduction programs, and a wide array of other experts. We developed a very different kind of drug fix label with very few words and a lot of white space which facilitate rapid comprehension. Also, we used a new visual aid, pictograms adjacent to the DFL, showing just five steps with explanatory text in the DFL cells next to it. The label on the slide is the example model drug facts label that we put forward with a placeholder for an injectable product.

After development, this was tested rigorously by an outside company that specialized in consumer behavior testing. The resultant label that was then made publicly available to companies to use in non-prescription naloxone development programs. They inserted their device specific information, did a modest amount of additional label comprehension and human factors testing and submitted their applications. Sponsors interested in developing a non-prescription epinephrine product could potentially

use some similar techniques and learnings from non-prescription naloxone development. Next slide, please.

But what if a company can't get there with labeling alone? Could they deliver the necessary information in another way for appropriate self-selection and appropriate use? Could technology be leveraged? Next slide, please. Well, now companies can. In May of this year, a final rule went into effect that enables a new approach. It's referred to as the ACNU rule, with ACNU being short for additional condition for non-prescription use. When labeling alone is not enough, something extra might be used to overcome a hurdle. To be specific, as noted in the bottom right bullet, the ACNU rule establishes the requirements for a non-prescription product with an additional condition for non-prescription use that an applicant must implement to ensure appropriate self-selection or appropriate actual use, or both, by consumers without the supervision of a healthcare provider. So what kind of extra are we talking about? Well, applicants could use any of a variety of means to augment labeling to get key messages across.

There's been a lot of public discussion about the possibility of use of apps, but other technology and even means other than technology can be proposed. We encourage creative approaches. So if a sponsor wants to come forward with a non-prescription epinephrine product, but study participants aren't getting key messages with labeling alone, a sponsor could perhaps propose an ACNU. We think ACNU has great potential to expand non-prescription options across a wide array of therapeutic areas. Next slide, please.

So what are some of the foreseeable challenges for development of a non-prescription epinephrine drug product? First, I want to emphasize that we want input from this workshop on perceived challenges, but here are a few possibilities. Epinephrine has serious adverse effects, particularly cardiovascular. It's given in a stressful emergency situation. There may be challenges in condensing that lengthy prescription label into a small but adequate DFL. The user might not read the labeling ahead of time and they must be able to figure it out quickly. Epinephrine is often given by the person experiencing the allergic reaction, but it might be given by a bystander with no prior experience with epinephrine.

And of course, there's always the possibility of unforeseen challenges, but I want to emphasize that despite challenges, we're very willing to work with interested sponsors in this very important area. Next slide, please. Finally, although I've been talking about non-prescription, we want to hear from you about a wide array of ideas for expanding epinephrine access, with a possible future non-prescription drug product being only one of the areas of discussion. Thank you. And I look forward to hearing what we'll hear as the day goes on.

Thomas Roades:

Thank you very much, Karen. And now we will have moved into our moderate discussion portion. Thanks again to both of our update presenters for great context here. Our panelists for this discussion session, please come on up and take a seat as I introduce you here. Our panelists joining us will be Carla Davis, Professor of Pediatrics and Chair of the Department of Pediatrics and Child Health at the Howard University College of Medicine. Also the president-elect of the American Academy of Allergy, Asthma, and Immunology. Then we'll have Alice Hoyt, leader of the Hoyt Institute of Food Allergy and the nonprofit organization, Code Ana. Next, we have Paul Greenberger rejoining us after his opening presentation, Paul, with Northwestern University, and thank you for pulling double duty here today. And then our two presenters from FDA will remain with us as well as one addition here. At the end of the lineup there, you'll see Kelly Stone, the Associate Director for Therapeutic Review in the Division of Pulmonology, Allergy, and Critical Care at FDA Center for Drug Valuation and Research.

Now, I'll give everyone a chance to give some brief opening remarks. Feel free to share a little bit more about your background and relevant work and thoughts on the topic at hand here for us today. We'll be

talking this discussion about some of the points that Karen raised in that last presentation, particularly how patients might be able to self-diagnose, self-treat, self-manage severe allergic diseases and anaphylaxis in a potential non-prescription setting. So I'll start it off with Carla, please kick us off.

Carla Davis:

Hello. It is an honor to be here with such a distinguished group of folks. I have several thoughts about the discussion, and I thought the last presentation was really quite thoughtful. I have a son with walnut allergy, and so I appreciate that when that's your experience, it can really impact the policy. I started the food allergy program at Texas Children's Hospital, and we led for a decade annually a patient education symposium is what we called it, where we educated families and the parents on all aspects of food allergy. But the one thing that I would say was quite interesting to me was that for newly diagnosed parents, and sometimes parents that had children that had been diagnosed a long time ago, the how to give epinephrine session and how to treat anaphylaxis session was always sold out with standing [inaudible 02:04:29]. And what that told me is that there is a lot of angst and a lot of misunderstanding among family members who we know have been educated at least once or twice and given EpiPens, but they still come back with continued questions and angst.

And so I think when I think about the parent or whomever in the moment, and it's likely that epinephrine would be sought at a moment when reaction is happening. I think we do have to be very, very careful about what information we give. And the other thing I might mention is that in a setting where there's a low health literacy, that's where I practice now at Howard University, lower health literacy, lower socioeconomic status of patients, I think this idea of having pictures of making sure that on a label for epinephrine, the terminology is not respiratory, that even that alone could be misunderstood. So there are quite many considerations I think need to move as we think about getting increased access for epinephrine. The last thing I'll say is I would underscore the complexity of the healthcare system and just the ability to get medications to our patients. And that is a huge issue that could potentially be addressed by really expanding the ways patients can get access to [inaudible 02:06:29].

Thomas Roades:

Thank you. Thank you very much. That really resonates. Obviously, myself have been educated before on [inaudible 02:06:38]. Thank you though. Yeah, I've been educated before by a healthcare provider, of course, about how to recognize anaphylaxis and when to administer epinephrine. But just in a preparation for this meeting, talking with many of you all, and in the lead-up, I was reminded of and learned a lot more about appropriate diagnosis and administration. So agree about the importance of reiterating all of these messages and making sure patients are educated. Alice, I'll go to you next for some opening remarks as well.

Alice Hoyt:

Thank you. And I just want to thank everybody for being here at an important meeting, and I'm very honored to be a part of this panel, so thank you all very much for including me. And thank you for sharing your story. I think a lot of us here have personal reasons that we're dedicating our professional lives to helping families stay safe when it comes to anaphylaxis. My husband has a peanut allergy, and so it's not surprising. I say God's vision is 20-20, as to why we walk the paths we walk. And so as an allergist, like many of my colleagues, I prescribe epinephrine all the time to treat anaphylactic reactions. I also prescribe epinephrine very regularly to what's called stock epinephrine, epinephrine prescribed to a school or a non-school entity to be used in case of an anaphylactic reaction either in somebody who

doesn't have their device or somebody who, as y'all saw the data earlier, they didn't know that they had a reaction, especially the case in young children.

They didn't know they had an allergy. And here they are in an early childcare setting, a school setting where a child is having a potentially life-threatening reaction, does not have a known diagnosis, does not absolutely have an auto-injector or an pre-dose epinephrine device to use to save that child's life. But because there is access to stock epinephrine, that school nurses, even non-school nurses are able to be trained laypersons with no food allergy, no anaphylaxis background at all are able to be trained on how to recognize anaphylaxis and how to properly use these generally very easy to use devices. I volunteer my time through Code Ana, which is a nonprofit. We've trained over 15,000 laypersons in how to recognize, respond to anaphylaxis. We're actively engaged in legislation to improve access to epinephrine, to emergency medications in general. So I'm very honored to be here and have so far very much enjoyed here Hearing from others too and learning from others. So thank you for having me.

Thomas Roades:

Thank you so much, Alice, and thanks for all of your impactful work on increasing access to epinephrine. And now I'll pass it to Paul. I know you had a chance to moderate in the opening session. Thank you for your work there, but now any thoughts more focused on the potentially non-prescription setting after you discussed the prescription setting previously?

Paul Greenberger:

Thank you. I appreciated the presentations we've had this morning, all of them. I have prescribed a lot of epinephrine for self-administration and patients with different conditions. I'm an intern. It's elderly people, non-elderly people, 12-year-olds and not. But some of our patients would report back that they used their own self-administered Epi as a bystander to treat somebody else. Often it was with a bee sting reaction where somebody was a crisis, but there's a lot of good if there's more epinephrine out there for close calls. And I think say there's value in having a population. And I'm talking about higher socioeconomics, lower socioeconomics, everybody. And it's important, especially lower socioeconomic groups, to make sure we're making an incredible impact to help there. And the second point, I just wanted to get it out there.

I focused a lot on whether epinephrine should be administered to patients with cardiovascular disease. 35-year-olds are having heart attacks, myocardial infarction with increasing frequency. So it really goes across the board age range. But from my career in allergy, which started in 1976, even before that, there were publications talking about cardiovascular complications of anaphylaxis, and I've seen it and we've reported some. But the failure to administer epinephrine during anaphylaxis has led to serious cardiovascular complications, specifically ventricular tachycardia, which can be life-threatening, and/or myocardial infarction. And every single practice parameter basically says the same thing. And I've been involved with other ones beforehand, and basically the language is the same, and that is essentially don't withhold the epinephrine during the anaphylactic attack, even if a patient has cardiovascular disease. And as you saw earlier, the epinephrine is metabolized quickly. We don't know what the T-max should be. We don't know what the C-max should be. We do know that it's important that it gets administered.

Thomas Roades:

Thank you very much, Paul. And then...

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Paul Greenberger:

... it's true.

Thomas Roades:

Thank you very much, Paul. And then before we get into our discussion questions, I'll give Kelly a brief chance to introduce himself and share any opening thoughts that he might want to share.

Kelly Stone:

First of all, I'd like to thank everyone for participating in this workshop, all stakeholders here and online. I think that Dr. Paterniti and Dr. Murry gave a nice overview of the regulatory landscape, both for prescription and nonprescription. And my participation in this panel really is going to be to answer any questions that come up from a regulatory perspective. And I'm not going to share my perspective so we can get to the questions at hand. Thank you, all.

Thomas Roades:

We'll jump right in then and thank you, Kelly. We're really going to take a patient-centered approach here and think through a lot of the same questions that we're discussing in the opening panel about how we diagnose allergic diseases, how we recognize when there's risk of anaphylaxis or when anaphylaxis is present, and then when and how to administer epinephrine.

Starting with the first point around, diagnosing allergic diseases, we heard about how providers approach this in consultation with their patients. In a potential non-prescription setting, how might patients or what would be the ability for a patient without medical training to self-diagnose allergic diseases that could put them at risk of anaphylaxis? Do you want to start on that?

Carla Davis:

Well, I'll start. I think it's going to be quite difficult. You heard that from the first panel. There are several non-anaphylactic, non-food allergic, drug allergic, insect allergic conditions that can mimic anaphylaxis. So it can be difficult. And I think that there would need to be significant education around that, if a healthcare provider was not engaged in the process. For someone who had never been exposed to an allergist or a pulmonologist, I think, asthma, this is another point I wanted to bring up. In the school setting, so, in Texas, we led the legislation for stock EPI, and when it was implemented, in a particular year, there were about 160 administrations, at least in the Houston area, and 80% of those were given to children, 20% to the adults.

But in looking at the descriptions of the cases, some of the symptoms could have been asthma exacerbation, and that is one of the biggest mimickers of, I believe, anaphylaxis. Is it asthma exacerbation or anaphylaxis? Epinephrine isn't unsafe in asthma situations but, I do think that it's going to be challenging. Or you heard about the viral infections, there are many things. I think, it's not impossible, but it would be challenging. I think having the green light by something, someone, right now as a healthcare professional, is something that would be very helpful.

Thomas Roades:

Asthma exacerbation, and then we heard from Hugh earlier about a number of other instances food-related that could present similar symptoms that could be difficult to differentiate. Any thoughts, Alice or Paul, would you concur with what Carla started us with there?

Alice Hoyt:

I agree that there needs to be education on what is anaphylaxis? What is an allergic reaction? What does it look like? And how do you treat it? But at this point, we are able to do that in a relatively efficient manner, and in a way that evidence does demonstrate laypersons understand people who have no medical training, who sometimes maybe have a GED, maybe have not graduated from high school, English is not their first language, and they're still able to learn in appropriately developed educational training programs. That when you see certain signs, that you are able to use an easy to use device to treat that, and then activate the emergency response system, which is very much calling 911.

When we're thinking about epinephrine for a very engaged patient family, whose families are attending the appointments. Who are going the extra mile in research and doing their own research, that is a very different audience than who potentially could be interested in obtaining epinephrine for other purposes. Such as, being that soccer mom who knows she's carrying three kids who have a peanut or walnut or an egg allergy, and she just wants to be prepared, but she doesn't have an allergy. But what if the kiddos forgets their medications?

All these types of things that a lot of members of the community are thinking about, and would like to have access to an emergency medication, pending that it's able to be administered effectively and safely. And I think we're at that point. I completely agree there needs to be education surrounding it, but I do think we're there.

Thomas Roades:

That's an interesting point you raised there around community settings that aren't necessarily tethered to a specific institution. Because I think we've seen, stock epinephrine, as you were describing in schools or other settings where there may be an elevated risk of anaphylaxis. But there are, as you were saying, carpooling to children's sports and things like that, instances that wouldn't necessarily be well suited to one specific location where epinephrine could be stocked. Paul, do you want to weigh in here on ability to recognize allergic diseases and when it would be appropriate to see epinephrine in a over-the-counter setting?

Paul Greenberger:

The first part is that, just like asthma, asthma can be overdiagnosed, it can be underdiagnosed, it can be undertreated, potentially overtreated, anaphylaxis as well. But, thank heavens, we have a lot of people that have been involved in this field for a long time or a shorter period of time, but they're getting the word out. I was thinking though, since the question came up if the product is over the counter, because, again, people's with cancer don't have anaphylaxis? And I would say the answer, yes.

I was working in academic center and I had a teenager who had repeated episodes of sudden throat closure, which, the person interpreted it was an anaphylactic reaction and had her boyfriend injecting her with epinephrine. It was out of control situation and we were able to show it was vocal cord dysfunction and it was not anaphylaxis despite many attacks. These are infrequent, but it could happen. But then it would be, well, how harmful, Dr. Murray, is epinephrine over-the-counter? But typically the effects aren't going to last very long. And I wouldn't think there would be a potential for abuse. I don't want to be naive. But most people don't want to have 10 or 15 minutes of shaking into tremulousness or rapid heartbeat. They're not seeking that because it's not a long lived effect.

But those are just some comments, but there can be misdiagnosis and [inaudible 02:20:01] I'm glad that the effort was successful for Naloxone, and I've looked at that to see how that might translate into the world of epinephrine.

Thomas Roades:

Oh, please go ahead.

Carla Davis:

I think the comments from Dr. Hoyt and Dr. Greenberger underscore that, with the right population, education can be extremely effective, and so I agree. And so I think, thinking about those patients that aren't in the moment in a reaction phase and have been diagnosed, has some exposure, especially even school teachers and those folks in that setting, they can be effectively trained for sure. And then thinking about the other population of patients who may not have had that exposure, coming into a CVS or Walgreens or some other store to get it in a moment, is I think something that should be [inaudible 02:21:09].

Thomas Roades:

Absolutely. Thank you. And let me just come back to the case that Paul was describing there around someone who was administered epinephrine, but was a different health event going on. Because we got a few audience questions about those points as well on the risk of misuse or abuse and an over-the-counter availability of epinephrine. And also, if anaphylaxis is incorrectly suspected and epinephrine is administered from someone who's acquired it over-the-counter, any risks on either of those points. And it sounds like, Paul, you were saying that the risk is relatively minimal in most cases. Do you want to elaborate on that and would anyone weigh in there?

Paul Greenberger:

I'm thinking, if the products that are regulated, approved for use now, that, yes, they could be administered for the wrong setting or incorrect setting. If it's a case of asthma, I go back whether there's a time when epinephrine was administered subcutaneously for acute events of asthma. That's what we did. And in those days, actually, for anaphylaxis patients, we taught them how to draw up epinephrine from the vial, or potentially break open two ml ampule, that I think is done outside the U.S. in Some countries. But then, is that really administered IM? It's probably administered Sub-Q. And that was, for example, treatment for asthma in the older era. And that was by and large tolerated [inaudible 02:22:53].

But I think, the benefits, the population would be greater than the risks, and I think that there'd be a large margin of safety on behalf of getting epinephrine to people.

Thomas Roades:

Appreciate that. Thought from anyone on the panel?

Julie Wang:

Yeah. And if we lean into the legislation that permits schools to stock epinephrine, it's not just it permits the school nurse or healthcare provider to do so, it permits anyone who's had training as defined by the state. And all states, except for Hawaii, have legislation that at least permit schools, so non-medical personnel, to recognize anaphylaxis and use these devices.

You point out something very important that there was an issue with a few years ago where some legislation actually just said epinephrine, that all legislation says epinephrine autoinjectors, and now we have other devices, other approaches to administering this lifesaving medication. I want to be very clear

that epinephrine would administer from a pre-dosed device, such as the ones that are approved by the FDA to be treatment for anaphylaxis, are incredibly safe.

When we are drawing up epinephrine from a syringe and administering it, with that method, that is where we can absolutely have adverse reactions. And I would never recommend that to be available to any lay person. And honestly, that really shouldn't be utilized in the healthcare setting for anaphylaxis, because of the risk of overdosing a patient and having a fatal response. But when we're talking about these pre-dose medications that have tried and true been used, they are generally easy to use, but yes, they do require some education on how and when to use them.

Thomas Roades:

Further thoughts there?

Kelly Stone:

I think those are great thoughts. And I'd agree that we gear it out in one or two doses, and Julie mentioned really that there's data there that vast majority state one dose. I think that there is a low risk of abuse for sure.

Thomas Roades:

All right. Appreciate those thoughts there. I want to follow up on use and particularly use of multiple doses potentially in just a moment, but we got one audience question I want to cover first while we're in the general category of diagnosis. And this is one that I think I will direct to Karen, on non-prescription availability. From the FDA's perspective, are you looking in clinical trials and an application to see actual self-diagnosis of a condition, or just recognizing that a reaction is occurring? If that distinction makes sense, would it need to be that a person can diagnose, "I have a severe allergy," or would it just be more a person can say, "I recognize what anaphylaxis looks like and one I would want to administer?"

Karen Murry:

The latter would definitely be necessary in the moment. We would have to assess via consumer behavior testing of a model drug fixed label, whether people or bystanders were correctly selecting to use the drug. But you bring up a good point, which is that, most of the time now when epinephrine is administered, the person has a diagnosis of a severe allergy that could result in anaphylaxis, and the non-prescription paradigm does not involve a healthcare professional.

Now, we have some kind of exceptions. For example, there is a non-prescription migraine combination oral product, and obviously a migraine is something that you think of as being diagnosed by a physician. But that issue of how important will it be that the person purchasing it or the person for whom it's intended, actually has a physician diagnosis of a severe allergy that could result in anaphylaxis. Now, I think there's been good discussion about the fact that when in doubt, administering epinephrine is probably the way to go. And also regarding the education issue...

I was the clinical lead on the Naloxone Model Drug Facts project, and one of the things we started with was looking with working with harm reduction groups that at that time were distributing a lot of prescription epinephrine in the community, usually under a standing order from a physician. And when we went in, we thought, oh boy, the education component is going to be so difficult, because, how are people going to recognize it? How are they going to know how to administer naloxone correctly? And we were very surprised to hear from these community groups that when they train people to who they were distributing naloxone, they found that people actually didn't need to learn a lot of information.

There were just a few key points that they needed to know, and then they would go out and use it correctly and lives would be saved.

There's not a perfect parallel between naloxone and epinephrine. For example, with naloxone, if someone looks at someone and they think maybe they're having an opioid overdose and they give naloxone, even if the person's not having an opioid overdose, they're not going to hurt them. And the question will be, and we'll need a lot of input on that, is what if that very situation were to happen in the non-prescription setting for epinephrine? If they come upon someone and they believe that they're having an anaphylactic reaction, but they don't know for sure, they give epinephrine and it turns out that the person wasn't having it, what's the likelihood of harm to the person to whom it's administered? Those are just a couple of considerations.

I don't want to take up a lot of time though, because I really want to hear from our non FDA panelists.

Alice Hoyt:

I would say that, as I alluded to the legislation earlier, we wouldn't have robust laws encouraging schools and non-school entities to stop these medications, if the risk of the medication outweighed the risk of giving it to somebody who wasn't necessarily having anaphylaxis. And to err on the side of caution when it comes to somebody potentially having anaphylaxis, is to give epinephrine from a pre-dose device and then immediately call for 911.

Carla Davis:

I would also echo that I don't think that the risk is going to be huge. Now, there is a risk, I think, of potential cardiovascular adverse events but, as Paul mentioned, that happens with anaphylaxis as well. But I think there's a difference between adults and children. Adults typically have more heart disease. And if you look at cardiovascular events in cohorts, adult can have up to 25% of these kind of events after having epinephrine, whereas in the pediatric population, it's really less than 3% typically.

As a pediatrician, when I have a child that has heart disease and I worry about prescribing epinephrine and I call the cardiologist, 100% of the time the cardiologist says, "Give the epinephrine and we'll deal with the aftermath because we want to save the person from anaphylaxis." I think that there is some potential adverse event, but I don't think it precludes the use of the medication.

Alice Hoyt:

I would just say my husband is an adult congenital heart disease specialist and pediatric electrophysiologist, and this is our supper time discussion. And he's always in favor of give the EPI, you would rather deal with a high heart rate than no heart rate. Which we know at the end of the day, if we do not recognize anaphylaxis promptly and treat it, what we're risking.

Paul Greenberger:

In addition, there could be drug interactions with epinephrine. Somebody who self-selects to use OTC epinephrine, and they're taking it along amino oxidase inhibitor, potential for acute hypertension. That's out there. Some tricyclics potentially, drug interaction could be a problem potentially. Again, the weight of evidence is to... I think that's yet to be figured out the evidence probably to administer the epinephrine in a serious condition that could go downhill.

I do want to point out that I was bringing up the issue earlier that, in the other session about acute hives at five or 10 minutes after, let's say, a known allergen. That you hope that the reaction is brought under control by epinephrine, right? You don't always know because, if the case is going to be life-threatening,

it's often going downhill very fast. And we know that many of the cases that I mentioned about, whether fatal, the death occurred by 60 minutes. We hope that isn't the situation, but you hope early on the case doesn't get worse. The situation doesn't worsen.

Kelly Stone:

I think this speaks to the fact that no matter what happens, we have to monitor and make sure that we're tracking the use as well as adverse outcomes if this moves in this direction.

Thomas Roades:

You all are doing an excellent job here on the panel. You've covered our next couple of questions without me even having to ask all of them, so well done. I'm going to keep us just a couple minutes past our scheduled time here to cover a few more topics that I think we're starting to touch on a little bit here. Was, I think you've all covered very well the risk of adverse events and potential content indications, how those could be handled, as well as the importance of monitoring afterward, contacting emergency services. I think, some of that would be information that could be conveyed on a drug facts label. We saw Karen gave us some examples there of what those look like. Any thoughts on what might be challenging to include there? Do you think the information that you all just covered would be relatively easy to cover on a drug fax label, or would there be anything else that would be particularly complicated to convey there? And welcome thoughts on innovative approaches there, as Karen described for us as well.

And then, along with that, if we could just briefly cover any thoughts on adult versus child dosages and considerations there. And if we're in a non-prescription setting, how we might handle having the appropriate dosage for different ages and sizes of patients essentially. If somebody has, say, an adult dose of epinephrine that they've gotten over-the-counter, how might they appropriately handle that if it's a child experiencing anaphylaxis? Would that be something that could be covered in a drug facts label as well? A lot there. Anyone want to all weigh in on that in the next five minutes or so?

Paul Greenberger:

I can comfortably give some advise, you know? They have a 0.3 milligram dose and the question should've been, is it indicated for whom and what else might happen?

Carla Davis:

Yes, it's a great question. I think that in the school setting, that question came up. Should we have a junior? What about elementary school kids? What about preschool kids or should it all be an adult dose? I think we landed on having both the doses in that setting, because, making sure that the pounds and the cutoff were very clear. I think, that that's something that should be... I don't know that that would be difficult to really put on a label. I think one of the biggest things that might be difficult would be, when to go to the emergency room. I think, that is something that patients constantly grapple with. I wanted to bring up just the economic impact of that. And I think, that the grappling of that, and Paul mentioned it, $1,000 copay, it has a lot to do with the economic implications of actually going to the emergency room.

Most of my patients, if they are scared, they will sit outside in the parking lot, because they think, "Okay, I'm going to get in here, and we'll see what happens." And I think, not going in has everything to do with, "It's going to cost me a bunch of money if I actually go in." And so, that's a tricky thing and I would be surprised, unless the reaction were extremely severe, that patients who took this over-the-counter would actually go. So if that is a consideration, we need to really address that.

The other thing I might mention is technology and how technology could be used to facilitate education around the use of epinephrine that was over-the-counter. I would love to see something that would check comprehension and make sure that a patient really understood what was going on, before they actually were able to access it and give it. And so those are my two comments.

Alice Hoyt:

I think the weight-based dosing part, the manufacturers have already made it pretty easy as to, this is the weight, this is the one you give. I think about, a lot of us have kids, young kids, it's middle of the night, we're trying to figure out that Tylenol dose. That's harder than figuring out, okay, this device very clearly is labeled for this weight, this is what I'm giving. But when it comes to putting things on a label, the label that was demonstrated for naloxone, I believe that was the device that was previously used for naloxone, that is the same device used in one of the epinephrine autoinjectors. We would be able to lean into what's already been created, and distill down the important information.

But I love the concept that the FDA is interested in creative approaches, to really take this type of access to lifesaving medication and training for it. Into really just a new era of, how our communities can be prepared for medical emergencies.

Thomas Roades:

Thoughts on any of this, labeling challenges?

Paul Greenberger:

And perhaps of age or heart disease, some heart disease, 1.5 milligrams might be the recommended dose, instead of 0.30 for some people with certain complications or comorbidities or potential drug interactions. I don't know if we're going to hear about this later, but I found the paper in the literature of ER care, how many people got epinephrine by age ranges every 10 years. [inaudible 02:39:04] teenagers, and then all the way up to 70 or more. But in the paper, it said that older meant ages 50 and older, so let's be precise when we talk about older.

Kelly Stone:

Dr. Murray has a [inaudible 02:39:23].

Thomas Roades:

Oh, please go ahead. Sorry.

Karen Murry:

I just wanted to provide one point of clarification. That naloxone model drug facts label was not for a specific product. During the testing, we just had to put in placeholder pictograms. We put one in for a possible nasal spray and one for a possible auto-injector, but it was not for a specific product. It was just you for purposes of testing.

Thomas Roades:

Understood. Thank you for that clarification. I know we've run a couple minutes long. I think we covered a lot of the content we wanted to get to and a lot of audience questions, so thank you all in the audience for submitting some great questions. I know we'll have a chance to get to some broader considerations around access this afternoon, and we've got a lot of audience questions queued up for

that. Before we run to lunch, any just brief closing thoughts from each of our panelists from what we've covered so far? Anything you want the audience to take home? You want to start?

Carla Davis:

We wanted to thank both of our FDA presenters for really a great overview of the history as well as the landscape. And I think it's an exciting time for us to be considering expansion of access. I think so.

Alice Hoyt:

I echo that.

Thomas Roades:

We got some more from Paul. Anyone from FDA want to give a brief closing comment?

Kelly Stone:

No. Other than, we appreciate all comments that were provided. This is a very helpful context for us, so, thank you.

Thomas Roades:

Absolutely agreed on that point. Thank you so much to all of our panelists for this session and to our FDA presenters and panelists.well, and that is-

Brian Canter:

We'll now turn to our optimum portion of the program. I'm Brian Canter. I'm an Assistant Research Director at Duke-Margolis. I'll be facilitating our public comment session. We want to thank all of our public commentators for their attention to this issue. We have our colleagues from the FDA planning team for this meeting and we truly value the input and appreciate taking the time to share perspectives for today. We're going to begin the public comment period of those who submitted recorded remarks, and then we transition to those who are selected for participation. Notified according to the timelines laid out in the federal register notice released ahead of the meeting. To ensure that we have time for all scheduled commenters to contribute and to ensure everyone has an equal amount of time to speak. I'll remind everyone to adhere to the three-minute time limit for opening remarks. I'll step in to keep us on time as needed.

For those who do join and have not recorded remark, please introduce yourself with your name and your affiliation at the beginning of your comment. And then I know many folks in the room and the virtual audience have further thoughts to share. I'll remind everyone again that the FDA has a comment docket open for this meeting, and the docket will remain open through January 16th, 2026. We encourage anyone interested to share further feedback in a written public comment. Now we'll begin with our first public comment, which is a recording from David Spangler, the Consumer Healthcare Product Association.

David Spangler:

Hi, I'm David Spangler with the Consumer Healthcare Products Association. We represent over 70 manufacturers of non-prescription medicines, dietary supplements, and OTC medical devices. Including non-prescription medicines for allergies or emergency overdose, such as epinephrine inhalers or naloxone. Access matters. Access is about time, it's about place, it's about removing barriers. One means

to wider access is making medicines shown safe and effective for direct consumer use, available non-prescription. What we term, prescription to non-prescription switch. When a product switches to non-prescription status, utilization typically increases by a quarter to a third. In a dramatic example, nicotine replacement therapy, utilization tripled in the first year after switch.

I've followed the switch process for many years. All non-prescription to non-prescription switch candidates, have to be shown safe and effective on the basis of their labeling. But few, very few, OTC medicines can truly save a life. OTC asthma medicines when immediate use may be essential, and the asthmatic can't access an RX medicine. Nicotine replacement therapy to extend the life of a smoker seeking to quit. Chewing an aspirin at the time of a heart attack. And that's a healthcare professional indication, not on the OTC label. Naloxone for opioid overdose. That's four. I could have missed one or two, but I can't think of others.

Epinephrine for anaphylaxis would be another. We've already made progress on epinephrine access, standing orders, community availability, or more methods of administration, for instance. So we are pleased that among the topics you are discussing today, is another step, non-prescription status. I hope we can finish the job of open access. As I said at the outset, access matters. Particularly in an emergency use situation, as is the case for epinephrine. Let's finish this job.

Ruth S. Day:

Hello, everyone. The topic is Anaphylaxis Outcomes: Cognitive Accessibility. I'm Ruth Day, Director of the Medical Cognition Lab, at Duke University, and former member of the FDA Drug Safety and Risk Management Advisory Committee. And I have served on other committees as well. Cognitive...

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Ruth S. Day:

... and have served on other committees as well.

Cognitive accessibility is the ease of which people can find, understand, remember, and use information and in a safe and effective way. Here's an example where directions look simple, but there are violations of cognitive principles. Therefore, we translated the original into an enhanced version based on various principles and then conducted experiments with participants who were adults in the general population with wide demographics. They studied either the original or the enhanced version on a random basis, and then we tested them. In cognition experiments, we tested attention, comprehension, and memory. In action experiments, we tested real world tasks.

Here's an excerpt from a cognition experiment where we asked among other things, what steps are needed to deliver the medication? And based on the results, we can calculate the percentage of participants who would actually get the dose. As you can see, only about 20% of those who studied the original instructions would get the dose, whereas those who studied the enhanced dose, about 80% would get the dose.

We also asked metacognition questions such as, if we gave you a test, what percent would you get correct? Everybody thought they would do well, about 90%, but that did not match actual cognition where the original group dropped significantly. So there's a big gap between metacognition, what they thought they knew, and cognition what they actually knew.

Here's an excerpt from an action experiment. We prepared videos where a demonstrator showed how to use the device, and in some videos he's correct, and in some, he committed an error. After each video, we asked, would he get the medication? Yes or no? When the error had to do with using the

wrong end against his body, the enhanced group did much better. When the error was using low force with a device against the body, which would not deliver the dose, again, the enhanced group did much better. So what conclusions and recommendations can we draw?

Cognitive accessibility of instructions is critical. People can be confident that they understand, yet be very wrong. They may use a device, yet not deliver the drug and not know that they failed. We must enhance cognitive accessibility using cognitive principles and conduct experiments on both cognition and action, set accessibility standards, and meet them. Thank you very much.

Brian Canter:

Thank you, David and Ruth, for those public comments. We'll turn to anybody in the room who was selected, [inaudible 02:47:57] the federal register notice.

If we don't see anybody in the room, and double checking if there is anybody in the online audience, but it appears not. We are running a little bit ahead of schedule, but from our morning sessions, it seems like we do have a lot to tackle when it comes to barriers to access. So we're happy to give some of that extra time to the next session and I'll have the opportunity to introduce the moderator there, Michael Pistiner, from Mass General Brigham and Harvard Medical School. Mike is a pediatric allergist immunologist and the director of the Food Allergy Advocacy Education and Prevention at the Mass General Brigham for Children Food Allergy Center. He also serves as an assistant professor pediatrics at Harvard Medical School.

And I might get a couple slides, I think, as well teed up.

Michael Pistiner:

Okay. Before I kick off our team, take about two minutes to just tie together a little bit of what we talked about this morning and then bring it into addressing some of these barriers in access now.

As we've all been talking about, anaphylaxis is a medical emergency with a simple lifesaving treatment, epinephrine. Yet access to epinephrine is anything but simple. Solutions for short people.

Access to epinephrine is anything but simple. Whether it's available, affordable, appropriately dosed, and actually used in a moment of crisis depends on a complex intersection of patient factors, settings, systems, and people. First, patient factors matter. Infants, children, adolescents, adults differ in weight, size, developmental stage, and anatomy. The correct intramuscular dose, 0.1, 0.15, 0.3, maybe 0.5, or intranasal dose, one milligram, two milligram, ideally align with patient age and weight. Delivery system design also raises considerations, including needle length for infants and individuals with obesity and intranasal fit in youngest patients. A one size fits all approach simply doesn't work.

Second, setting matters. Anaphylaxis can happen anywhere. It happens at home, in daycare, at schools, in restaurants, on airplanes, in houses of worship, sports venues, you name it. Each setting presents different challenges, who is present, what devices are available, how quickly epinephrine can be accessed, and whether someone feels empowered to act.

Cost and availability remain major barriers. Many families are asked to purchase multiple epinephrine delivery systems for home, school, travel, and alternate caregivers, often with inconsistent insurance coverage and prior authorization requirements. Schools, daycares, emergency responders, healthcare facilities, and public venues face budget constraints that may limit stocking and training. High costs alone can delay filling prescriptions or replacing expired devices.

Training and preparedness are also critical. Knowing when and how to give epinephrine requires hands-on teaching, refreshers, trainers, written action plans. Without this preparation, fear. Fear of giving

epinephrine too soon, fear of needles, fear of causing harm, fear of legal consequences, fear of downstream healthcare costs can delay and prevent appropriate treatment.

Finally, advocacy underpins everything we're discussing today. Policies that support affordable epinephrine, stock epinephrine in schools and public spaces, good Samaritan protections, standardized discharge education, and guaranteed access upon emergency department discharge can directly influence patient outcomes. Ensuring ready access for all requires addressing patient needs, economic realities, training gaps, emotional barriers, and policy solutions together.

So as our team gets together, come on up, guys, we're going to try to hash out some of this stuff with you guys. So get your questions ready and we're going to get fired up. Joining us virtually is Ruchi Gupta, Professor of Pediatrics and Medicine at Northwestern University Feinberg School of Medicine. Also participating virtually is Christopher Warren, Assistant Professor of Preventive Medicine and Director of Population Health at Northwestern University Center for Food Allergy and Asthma Research. Here with us in DC is Linda Herbert, Associate Professor of Psychology and Behavioral Health at Children's National Hospital, Director of Psychology, Research and Clinical Services for the Division of Allergy and Immunology at Children's National. We also have Charity Luiskutty, a physician assistant at Children's Specialty Group Allergy and Immunology at the Children's Hospital of King's Daughters and an advocate for the FAACT team. And Kelly Cleary, Medical Director and Vice President of Health and Education [inaudible 02:53:51].

Are we ready? All right. Very good. So this one will go to Ruchi.

Ruchi Gupta:

All right. Can you hear me, Mike?

Christopher Warren:

Loud and clear.

Ruchi Gupta:

Okay. Awesome.

Michael Pistiner:

By the way, when I say this one goes to Ruchi, you got three minutes. Go.

Ruchi Gupta:

Oh. All right.

Christopher Warren:

I can kick it off if you'd prefer, Ruchi. I've got a few remarks.

Ruchi Gupta:

Go for it, Chris. I'll go after you. I'll follow you. That sounds great.

Christopher Warren:

Great. Perfect. Ruchi and I work together at CFAAR, so I'll kick this off. And while Mike mentioned my credentials and while I am junior faculty, I've been working with Dr. Gupta and our colleagues at

Northwestern studying food allergy and anaphylaxis access management for nearly 15 years in a bunch of settings, including schools. Since my primary training is in epidemiology and my research interests lie in population health, I think my role on this panel is going to be to provide some epidemiologic perspectives for the panel. And given that I have some experience alongside Dr. Gupta leading some large US population-based studies that have aimed to understand epinephrine access and utilization to try to advance anaphylaxis management in the broad US context, I think we'll talk some about that. And that is, of course, when we talk about US population-based studies, we're talking about from the little bitty babies, through adolescence, into young adulthood and all the way across into our older Americans.

As we dig into the data during this session, it's really important to highlight a few themes, I think, upfront in terms of available peer reviewed data relevant to understanding epinephrine access across the US population. You can't help but notice that it's mostly a hodgepodge of single site studies relying on largely data captured by EHR records during specific time windows. And while those studies are generally very well done and informative, they're almost exclusively conducted at some of our country's leading medical centers, and therefore we assume that they reflect an upper bound or optimistic estimate of epinephrine access at these well-resourced institutions. But the mostly unexamined assumption is that when these studies conclude that fill rates, availability during reactions, successful utilization is suboptimal, that it's likely worse in other settings. But the truth is, given the current state of the data, we really don't know.

And broadly speaking, besides this EHR data, the other main body of research addressing these topics includes some very large survey-based work by our group to try to understand food allergy prevalence and management that captures historic data on adult and pediatric patients' epinephrine use and possession of current epinephrine prescriptions at the time of the survey. We've also published a deep dive on epinephrine carriage and utilization in 2018. And there are also a smattering of insurance claims analyses that have been published over the past decade plus.

But you'll notice that most of these data are at least five years old and often 10 to 15. And this is important because, as we've been discussing today, the epinephrine landscape has really changed and seems to be changing more and more rapidly every day, not just in terms of new devices and delivery modalities coming out and generics, but also with respect to how action plans have changed from recommending reflexive activation of EMS upon utilization of a delivery device to a more patient reaction specific approach, which now increasingly recommends more proactive epinephrine use before reactions progress to full-blown anaphylaxis.

All that said, I just want to say as we dive into the data today, I hope we can land and identify some shared key knowledge gaps and start aligning on how we can work together with all these amazing individuals who we've been assembling here at this amazing event and start working together to fill them.

Ruchi Gupta:

Great. Thanks, Chris. That's great. The epidemiologist should start out.

Hi everyone. I am Ruchi Gupta. I know so many people that I'm seeing on camera. I've been enjoying this so much. Thank you so much for the invitation and thanks Mike for leading this session. I really want to tell you a little bit how personal and professional this is for me. I have been studying food allergies just a little bit more than Chris, about 20 some years and got into it because of a patient. And at that time, we didn't have any data on prevalence, public health impact. And so that was one of the first studies we conducted now at CFAAR and we've continued to really understand the impact food allergy has, 33 million Americans, one in 10 adults, one in 13 kids. It's a lot.

As we published that data, the first thing that happened with the one in 13 kids was two in every classroom. So when we talk about schools, it's really very important. Now, I soon after starting this, my daughter was born, playing with my son eating a PB&J and lo and behold, I became a mom of a child with food allergy. So as I've lived it with her, I have also seen access issues. I'm also a pediatrician and I'm a professor at Northwestern and I am the director of the Center for Food Allergy and Asthma Research. And a lot of this just came out of personal interest and need to make the world better for everyone with food allergies and learning it on a firsthand basis.

As we started studying it, I just want to mention another story because I love storytelling, is while we were studying it, a child in Chicago, eighth grader, in school at a holiday party around this time had an allergic reaction. They ordered Chinese food from outside and there was no epinephrine. No one had it, no one could access it. By the time they called 911, that child had died. This became a massive initiative in Chicago that we were fortunate enough to be a part of and help support where we wanted stock epinephrine. And Chicago Public School Systems became the first large school system, third largest in the country, to have access. CPS said, "We will never let this happen again," and provided access to epinephrine for all schools.

It was expensive, it was done, and it's changed a lot over the years. I do want to bring that up in terms of access in schools, in daycare centers, and colleges, and restaurants, and airplanes. There are so many places, but biggest thing is as a pediatrician, individual access is challenging, primarily in the Medicaid population. A lot of times the devices they get are not easy to use. They don't have access to the more sophisticated, easier to use, newer devices. Even though in Illinois, I think the two new epinephrine auto injectors or devices have now been approved, but there's still a lot of steps to getting it to our patients.

I can stop there as I think I've used up my three minutes, but thank you all for talking about this. This is something very near and dear to all our hearts.

Michael Pistiner:

Thank you, Ruchi. Let's take it from Linda.

Linda Herbert:

Sure. All right. Thank you so much for having me. I was thinking a little bit about what Mike had posed to us, which is what is our secret power on this panel? And I'm a psychologist. I work at Children's National right up the street with a lot of patients, a lot of kids, a lot of adolescents, a lot of caregivers of kids that have food allergy. And so I think I can speak as a licensed psychologist, one, to the feelings about anaphylaxis and epinephrine use, and then also as a health psychology researcher to how do people make decisions and what is really contributing to health behavior.

We can, of course, delve a lot more during discussion into each of these things, but from a licensed psychologist perspective, the feelings and things that I'm hearing from families are fear about using epinephrine, about when do I use it, what will happen when I use it, what will happen if I do it wrong. Uncertainty. Again, when do I use this? What will happen? What's going to happen if I teach someone else and they don't know how to do it? Am I doing it at the right time? Things like that. And just this prevalent worry and misunderstanding about the nuance of food allergy allergic reactions and when and how to use Epi.

And then when I think about things as a health psychology researcher, I really lean into theories. When we think about using epinephrine, first, we need to make sure that people know how to use it and that they have the skills to use it, and that in the moment they have the confidence to use it. As health psychology researchers, we like to lean into what's called the health belief model, which tells us about interpersonal factors that determine if a health behavior is engaged in. Some of that are things like, how

severe do you perceive the thing that you need to do? How severe is your food allergy? How susceptible do you think you are to a severe allergic reaction? And then what are your cues to action if you experience an allergic reaction? What are the things that are going through your mind? What are the things that your body's feeling? And then what are also the environmental cues? What is happening around you that might either promote or prevent you from using Epi?

And then what are the perceived facilitators and barriers to using it? And do you have the self-efficacy and a social environment that's supportive of using Epi? I think that these intrapersonal factors are really important, but that social environment, this queue to action in the environment, is really important as well. And so for that, we can lean into looking at social determinants of health. Do you have health literacy? Do you have information available to you in your language? Do you have a community where you can get an epinephrine autoinjector easily? I was thinking a lot about what Dr. Davis was saying about how far you have to go to get to a pharmacy. There's all these other factors that then play into what actually happens in that moment. I'm happy to add that perspective as we discuss today.

Kelly Cleary:

My name is Kelly Cleary. I am here from FARE, so I'm the medical director at FARE. First, thanks to the Duke-Margolis team for convening this and the FDA. This is such an important conversation and I loved hearing everybody speak this morning. And thank you for having FARE here because Mike didn't ask me my superpower, but that made me think about it. As my superpower, I think I am here as a parent of a food allergic child. I am a pediatrician trained in emergency medicine, so for many years, not currently, but for many years, took care of those kids coming into the ER and then really today here as part of the patient voice. Because part of what we get from FARE are the stories that are coming in and some of the struggles and challenges from families. I think that what we hear consistently is that affordability is not consistent and access is not always equitable. And as Linda said, hesitancy is actually something that is really common.

Mike asked me this morning to just give a brief overview of how Epi use in community settings, what is the landscape now? Not a big topic. Mine is going to be really quick. But in looking at community settings, I really look also at that individual, those decisions that are used in the individual level, because it actually shows us why stock Epi is necessary in public venues, that hesitancy, the not picking up prescriptions, and then carriage rates, when we look at who's actually carrying their Epi when we would like them to be.

Mike had asked me to just start with airlines, so I will just give a very brief what's going on right now with airlines. There was a paper in 2013 that looked at the incidents of airline allergic reactions. They found that two to 4% of the medical in flight emergencies were due to allergy and about 5.5% if it was someone less than 18. I bring in the quality of life there because as an allergy parent, it's not just about having a reaction in the air, it's about what goes into flying. The anticipation, the anxiety, the wiping down the tray, the knowing that I'm going to read every food label while I'm there, and then the fear of having an allergic reaction 30,000 feet above.

Currently, the FAA requires epinephrine to be in those emergency medical kits. However, if anyone has ever been the doc on board where is there a doctor, I'm hoping that it's back pain that I'm being called for and not that I would have to be extracting from a vial the proper dose of a one to 1,000 or a one to 10,000 solution. That in and of itself, there have been smaller looks at how long it takes ER nurses, versus physicians, versus parents to actually draw a correct dose from those vials. An ER nurse can do it pretty quickly and they can do it under a minute, but other physicians are showing closer to two minutes and parents closer to five or six minutes, and that's when every second counts.

The 2024 FAA reauthorization has a clause in it regarding food allergy and protocol and medications that we are going to take another look at what's in there and reconsider and within two hours evaluate those... Two years, wish hours, evaluate those protocols. But it's not a mandate or a requirement that there is a different form of epinephrine that would be easier to use for people who are not trained in medicine. So I think that that's an important part of airlines, and I know we'll talk more about airlines.

Schools are another big community setting. I know Ruchi began to speak of schools, and we know that the 2013 School Access to Emergency Epinephrine Act is one of the first things that we had seen that actually allows for stock Epi to be in school. As Dr. Hoyt had said, this is now used in all states except for Hawaii where it is allowed to be in schools. Now, the caveat there is that that doesn't mean that it is required in all of those states. So leveling that consistency field is important. I think Mike and I have been on an expert panel, actually a couple people in here, Julie and Linda, on food allergy management in schools, which was a project of the CDC and AAP and really looking at how can we do a better job there. Even when Epi is potentially stocked, where is it stocked? How is it stocked? Who can access it? How far is it from those kids? Is it in a locked environment?

And then when you look at schools, that is not necessarily covering beyond K through 12. So that's where entity laws come into play. And in looking at entity laws, that would be laws within restaurants, public places, arenas, theme parks, but also stuff like preschools or colleges, which really dictate an entire other level of how we handle food allergy. I could go on, but I will stop and let us discuss it later.

Charity Luiskutty:

Hi, I'm Charity Luiskutty. I'm here on behalf of the Food Allergy and Anaphylaxis Connection Team. I'm here, like many others, as a practitioner and also a parent of three food allergic children and a wife of a food allergic adult, which brings me into this space as well. I'm here more bringing a patient advocate voice to this table. I've been part of... as a support group leader, and I'm doing pediatric allergy right now too, so seeing the accessibility issues in obtaining the prescriptions for epinephrine and such. I was actually asked just to touch on... I'm in the Norfolk Virginia area too, so I see a lot of the military population, families in the military, and so asked to touch on that a little bit too. And so one thing that I just want to touch on is accessibility that we see in the military and civilian population.

One thing that isn't super specific to this conversation, but a little bit is maybe accepting an initial diagnosis of food allergy and how that might impact people's quality of life, accepting that and needing to accept the fact that now caring epinephrine is going to be part of what they need to do. Part of that may be how that might impact career roles, just their life in general. Part of that might also be affordability and accessibility of keeping epinephrine with them, obtaining it. So those are some issues that come to mind too, but that's part of getting that correct diagnosis, accepting that diagnosis.

And then from a patient perspective, and then as a practitioner too, I see issues with the delay in getting that initial prescription, and we've talked about that as well. You can prescribe the medication, but then how long is it taking for the patients to obtain that prescription? So there's barriers there. There's barriers when they do finally get a prescription, is it what they were trained on in the office? They may not be comfortable using the medication that you actually prescribed. You might have talked to them about how and when to use or how that medication should be used, but then if they get something from the pharmacy, take it home, they're not comfortable using it. So there's barriers with their comfort level or understanding on how to use those devices.

Sometimes if there's a delay in obtaining the medication, cost. They might be told there might be some time before they can get refills. We've seen that when there is a reaction, they may hesitate using the medication, worrying that maybe it isn't bad enough, how long will it take me to get more medication? Again, worry in obtaining more medication. So not just fear of using it, but the accessibility and

affordability issues as well. There should not be concern about these things because we know that the time, there shouldn't be a delay in using the medication. All these issues have come up and that fast, decisive use of the Epi saves lives.

I appreciate the opportunity to come here and discuss these barriers and how we can improve this access. I'm here on behalf of FAACT, and part of what we're doing in other organizations here is trying to empower and educate and advocate with the patients and in the community, to educate, legislation. We do a lot of school education, free of charge, civil rights advocacy, that we provide free of charge for a lot of families that are single income. We've helped over 7,600 families with their 504s from school age to college, trade schools, adults in the workplace, and bringing together people in the community so that they're not doing this alone. We look forward to hearing on this conversation with y'all. Thank you.

Michael Pistiner:

Does anybody have any final points they want to make before we do some thunder dome? Ruchi, Chris?

Linda Herbert:

I have a little thing. I should have also referred to my notes and brought up stigma as well. One of the things that I hear from patients is also just the stigma of carrying epinephrine and what that looks like and how they're perceived by their peers. I do so much work with young adolescents and older adolescents.

I have a research project right now where we're studying whether or not an intervention helps them become independent food allergy managers, and a big thing that comes up is social communication about their food allergies and how they're navigating disclosure. When we think about whether or not someone gets access and gets Epi used appropriately at the right time, part of it is did they feel comfortable having the people around them knowing that they even have food allergy and that they have an epinephrine autoinjector with them? I didn't want to forget that.

Ruchi Gupta:

Can I follow up on that real quick? Because I do think it's super important, just people, the usage of Epi even in a reaction. I'm so glad this morning everyone just talked about if you're worried, just give it because there are so many obstacles I feel like and stigma is so... You're 100% right. Especially in teens and even college age kids, carrying it is challenging, but then during a reaction knowing when to use it and how it can benefit you so quickly. We're talking about access, so just getting it. But even after you get it, there are quite a few steps to effective management of anaphylaxis. Let's get back to getting it. Go for it, Mike. Sorry.

Michael Pistiner:

Well, what we're going to do is we're going to break up our time into different settings because as you all already envision, there's going to be different access issues depending on the setting. We're going to kick things off with the home and the primary care, and we'll start breaking down some of the discussion topics there. Then we're going to move to preschool, school, university. Then we're going to move to public places and/or airplanes, and then we'll close things up.

We'll kick it off with the home. And these four questions we're going to keep applying to the different settings. What is the current state of patient access to epinephrine and are there differences between adults and kids? What are the barriers to epinephrine access and use? Discuss available data regarding barriers to epinephrine access. The third, how previously implemented efforts impacted access to Epi?

And the fourth, what role have state and federal legislation played in enhancing patient access to epinephrine in those settings? We'll keep applying those to each of the different settings.

All right. Some of the issues that came up with the time of initial diagnosis and then someone writing a prescription for epinephrine, that was brought up. As many of us know, there are many forms of epinephrine. And if a prescriber prescribes what they think...

PART 6 OF 10 ENDS [03:18:04]

Michael Pistiner:

And if a prescriber prescribes what they think is the form of epinephrine that they want to give to a patient, they don't necessarily get it at the pharmacy. And there's some uncertainty what is going to be insured, there's some uncertainty, how much is it going to cost? And this can vary from state to state, from local pharmacy to local pharmacy. I just want to kick that conversation off here.

Kelly Cleary:

I can start us off on access. I think one of the things that we hear about often from FARE is when someone may go to the pharmacy, and as Charity had mentioned, what they are hoping to get is not necessarily what they get because of coverage. So that's something within the home that we hear of families that would like a particular method of delivery, and that's not what they're getting. So that's one that we hear.

And then another true mission part of FARE is that we are trying to bridge some of the disparities that we all see within food allergy. And one of our large initiatives is called the FARE Neighborhoods Initiative, where we have seven sites throughout the country in zip codes that are those that have lower incomes and more need for services. And what we found there is that access to even getting an epinephrine prescription to begin with is difficult because they're not getting into a doctor and being properly diagnosed.

Then once the epinephrine is in hand, we're noticing that or we're getting data that [inaudible 03:19:43] rates are low and the knowledge of how and when to use that epinephrine is low. So I think that on the access level within the home, those are some issues that come to mind.

Linda Herbert:

And I would add, it's not just can you get the advice that you want, but can you get as many as you want? As we know, families are composed of many different constellations. And I routinely am talking with families just about, "Well, how do we make sure that the epinephrine autoinjector goes from one home to the next and back again?" And so families really sometimes struggle to make sure that they have enough devices. We haven't gotten to the school setting, but making sure that they have one for the school setting, perhaps they want one at the grandparents' house. There are many, many, many reasons to have more than one, two set.

Michael Pistiner:

And then those very same families then need the confidence to be able to train the other people that they're passing the responsibility of the child to. So they need to be thinking about ways that they're going to train there for other, grandma, people who may not necessarily take them very seriously.

Kelly Cleary:

Which is why this comes full circle, because if that said grandma takes them to a restaurant and forgets the epinephrine at home, if there were stock epinephrine available with people who know how to use it, then that child could be treated if there were an allergic reaction. So I agree.

Michael Pistiner:

And then maybe-

Ruchi Gupta:

I was going to back up a little to just access and number of people with food allergies. So we talked about one in 10 adults have a convincing food allergy, but one in five in our survey, and Chris knows this better than me, but one in five actually checked, yes, I have a food allergy. So one in five adults are avoiding a food thinking they have a food allergy. Now, if I was there, I would ask, what percentage have a physician diagnosis? If anyone wants to guess, but I'll just tell you, one in 20. So 5% of adults actually are getting a diagnosis, but 20% of adults think they have a food allergy.

So that is cutting your numbers right there. And if you take the 33 million and one in 10 adults, half of them are getting a diagnosis. So they're not even going to the doctor to get epinephrine. And then for kids, it was about 5% of kids actually have a physician diagnosis. So now you're talking even lower numbers of how many are getting diagnosed, and then how many of those physicians are giving them epinephrine? Because what we also know is only 0.6% of the Medicaid population is diagnosed with food allergy, has a diagnosis. Why? Because they probably aren't getting to the allergist who is the one who gives them that formal diagnosis.So you're going low on your numbers now to how many can even access it from a physician as we're talking about making this OTC.

Now, once they get to their primary care ... And now let's get into primary care because you mentioned that, so once you get into primary care, how many of those primary care family practice pediatricians are waiting for them to go to the allergist to get it versus prescribing it themselves? And I'll tell you in a busy pediatric clinic, it is not easy to get patients epinephrine that they want. You are pretty much writing a generic prescription and that will get filled by probably a generic version, which I can tell you is not what we train them on and it is not as easy to understand and use.

We do have coverage for patients for the other devices, but oftentimes they require prior auths or some kind of more sophisticated paperwork that primary care physicians just don't have the time and staff to get done. So I'll stop there, but I want to back up to just basic access and how many are even getting to a doctor to do this.

Christopher Warren:

Yeah, maybe I can-

Michael Pistiner:

[inaudible 03:23:47].

Christopher Warren:

Oh, go ahead. I was just going to say-

Michael Pistiner:

[inaudible 03:23:48]

Christopher Warren:

... I could build off that a little bit with a little more context for the whole kind of age spectrum because we're talking about what's the state in children versus adults. And even children are far from a monolith. When we look at rates of those folks in our national data who do report not only a convincing history where we believe it is an IG mediated food allergy, but then also say that they have a physician diagnosis. Across all kids, you see just over half to well under two thirds say that they have a current epinephrine auto-injector prescription. And those rates are highest in that kind of five to 13 school age population.

Now, as you go into adulthood, those rates drop a lot with essentially like a linear decline up into the older age groups. And so we obviously, I think pediatricians and pediatrics is kind of overrepresented on this panel, but it's how food allergy management is happening in older adults in the US is a bit of a black box. And we know there's a lot of adult onset food allergy happening and we suspect that those adults who are developing allergies later in life, we simply don't know their risk profile as well as these kids, but we know that they're not. They might be particularly at risk of going without epinephrine.

So I think I'm glad that we're taking this sort of life course framing because there's different challenges at each developmental phase. And I'm sure Linda and others can talk to the unique challenges of food allergy management in adolescents when we know they're at higher risk of engaging in risk taking behaviors and less likely to carry even when all the other pieces are in place where they have the right device and they're well-trained and they know what to do, they simply might just not have it or be willing to use it when they need it.

Michael Pistiner:

And a question just actually came in addressing the beginning of the journey in the emergency department. And so one of the things is time of discharge. So if someone does experience anaphylaxis, they're treated, then at the time of discharge, is it possible to get epinephrine in their hands for that car ride home? And it does potentially change behavior on the part of the discharging team. If it's after hours, there's no available pharmacy, that family then doesn't have an epinephrine dose available in case they have a biphasic, then they might be observed for longer, potentially admitted. So these are things also to think about, are there ways and systems upon discharge from an emergency department that perhaps people can go home with epinephrine in hand?

Kelly Cleary:

And teaching at that point, because I think that thinking of a busy ER and discharging patients, having someone have the time to sit with a newly diagnosed family to tell them how to use epinephrine, when to use epinephrine, and I think that that's another component. And we know that there are a lot of patients right now who are using emergency rooms and urgent cares as their primary medical home, so that's where they're getting their information. So really ramping up the way that we monitor how they're leaving, and if they're leaving with epinephrine and directions in hand, I think that that's something that would really have a significant impact for a lot of the community.

Linda Herbert:

There are actually studies too that show that one of the highest predictors of using epinephrine when it's needed is actually having education about it. And that might seem like a very common sense idea, but that is what the data is showing. So it's really key. A trend that I've also noticed is to no longer get trainers when you get your prescription. I'm not sure how many of you guys are noticing that, but we

now, I routinely ask families, do you actually have a trainer to go home and practice this? And many of them say no.

And we now, I have one of my research assistants contact all of the different epinephrine autoinjector producers, and we make sure that we have a stock of trainers on hand so that we can give them to families immediately in clinic. And every participant in my research study gets them sent home to them as well because we just know how crucial that is to not only making sure you know what to do, but having a way to teach other people as well.

Charity Luiskutty:

Yeah, I think that was really important when you were saying you have to be comfortable enough to do it yourself and train other people because that becomes your responsibility, especially when the children can't advocate for themselves until they're old enough to do it themselves every single time you hand off that child to someone else, unless it's a school where you're trusting they're trained or they've been trained properly, that's your responsibility to hand that off.

And it was said earlier how when you, I forget your name, I'm sorry, but when you held the conferences talking about how and when to use epinephrine, those are the most well attend sessions. Allergists have only so much time to spend with the patients or the nurses in the clinic, and it's just amazing how many times patients will come back and yet they need to hear that and they want to hear that over and over again. So I think increasing the accessibility to education, that's where different organizations come in and online education and resources are so important for patients as well. So they become comfortable with that.

Linda Herbert:

And educating more than once. So again, I'm talking a lot about adolescents because I work with so many, but what I find is that adolescents diagnose when they're little, they don't know as much as you think they do or as much as they think they do. And one of the key components of some of our work in clinic is to provide that foundational food allergy education. Dr. Sharma, who was here earlier, he's reviewed all of the education that we provide to make sure it's accurate, but we really provide that because if you consider that that 13-year-old was diagnosed when maybe they were six months or 12 months, they are not the ones that were the recipient of that education to begin with and a lot has changed. So it's really important to routinely be talking and providing access to this education.

Ruchi Gupta:

And I also just want to ... Oh. Sorry. Kelly, go ahead.

Kelly Cleary:

And I also think it's ... Sorry, Ruchi.

I was going to say that I think there is a little bit of nuance that we even heard this morning with some of the questions on, would you give epi now? Would you give epi now? Well, that actually gives me comfort as a parent to hear because that is what is happening in parents at home. They are having some different things in their head like, "Maybe I should, maybe I shouldn't." But it is because there's a little bit of nuance. And I think that lots of the community that we speak to, they know when it's a severe reaction that they're going to give epinephrine, but it's in that lead up that there's always questions. And I think some of that comes down to nuance. And when you're newly diagnosed and hearing this information for the first time, you might not be able to digest all of it. And it does need to be repeated over and over.

Ruchi Gupta:

I mean, I'll follow up on that and then I just have one more thing. I think the anaphylaxis definition I think Julie was talking about this morning that's been revised is great because forever we were talking about these two organ systems and anaphylaxis and the difference between that and regular reaction. And I think we complicated it a lot. And we also, just like Carla, have had sessions with families where we ... Well, now we'll have a grapefruit, now we have new devices so we can do other things. But we would have a grapefruit and all the epinephrine autoinjectors and have families use them and have the kids use them. And we really promote this even for families to do with their kids, but teaching them, once they use it, they get so much more comfortable with it and they'll use it earlier.

But just personally, and you all have these stories too, but when my daughter was young, we've used pretty much every device and she would be so scared. And then I would stare at her, we'd call it the stare because you're watching for these reactions and when they come and it stresses them out even more. But once you've used a device a couple times, you're not scared anymore. You're ready, you're prepared. And that's what I think we even talk about having them use it during oral food challenges or during OIT or treatments really makes them so much more comfortable just using it quickly at the sign of a reaction.

And then the other thing I was just going to say is disparities because we were talking a little bit about ... We also conducted where actually, Chris and some of our other colleagues were all working on a new economic study. So we're going to have new economic numbers for you very soon, but our old numbers, even in our old numbers, it was $24.8 billion a year. And most of that is on the family. And when you look at differences by income, our low income children were going to the emergency room, spending double on emergency room visits, then higher income children, less on allergist visits, less on medications, including epinephrine. And I know we've come a long way with the cost in getting them the generics, but they were not getting them in their hand. And they were much less likely to use an epinephrine autoinjector before going to the emergency room. So there are significant roadblocks for families and especially our low income families to access epinephrine even now.

Christopher Warren:

Yeah, that's such a good point, Ruchi. And just to build off of that, there was a nice study conducted in a New York ED to the point of dispensing upon discharge where folks who were prescribed, they presented for anaphylaxis, were sent home with a prescription for epinephrine. About 85% filled their prescription, but then when they checked back the following year to see, well, do they actually have an unexpired epinephrine injector on hand, only 40% did. And the big predictor of whether or not they did or not was, were they at that point getting care from an allergist? Did that kind of handoff happen where then they go from showing up to the ED to actually getting more proactive management?

Now, it would be interesting to see if they had good primary care, what sort of multiplier that would lead to. But I think there's just all these handoffs that we need to be cognizant of and sending them home with the prescription isn't enough, even though it's certainly better than not.

Michael Pistiner:

Okay. We'll move settings. Now when the child or whoever it is who isn't in the care of the parents or their caregivers now passes off responsibility to others, now they have to trust that those other places and institutions are trained and that there's epinephrine accessible. So let's kick it off with K through 12.

Kelly Cleary:

I'm happy to start. We at FARE last year did a project with the AAP where we looked at 10 schools who received grants from the AAP to start to implement some of the food allergy management school guidelines. And it was really small steps toward doing it. But what it opened my eyes to was that out of those 10 schools, there was no consistency on what each school was doing. And there were some schools who were still at the level of needing to be able to identify and document which kids in their school had food allergies, but then there were some schools that were much ahead of that and really thinking about, what do I do before school, after school on the bus?

So really the lack of consistency there I think is a worry as a parent because you are as a parent often going into the school at the beginning of the school year with your list of questions that are there to just keep your child safe. So I think the lack of consistency sometimes in K through 12 and schools in general is something to note.

Michael Pistiner:

And then just a couple general things to be thinking about in the school environment is that school staff, school administration, school health needs to be thinking of the known and the unknown. And so data has consistently shown that about 25% of epinephrine administrations are to folks who are not known to the school. And as was mentioned earlier, even some of those are adults, staff, and visitors. And so the school staff being trained to not only manage the known folks in the school with an allergy, but also to be able to have a system in place, to have stock epinephrine available to treat the unknown, but then also be ready and train others to potentially treat the known.

Ruchi Gupta:

I was also going to ... Absolutely. And this is just an amazing discussion. I was going to also mention even after this push to have stock epi, one thing, right after that happened in Chicago, I started writing the prescriptions because the big thing is who's going to write the prescription. And we have struggled with this in Chicagoland because after a while, because we're part of these large academic institutions, we couldn't write them anymore because of liability, because you're writing them to not an actual person, but to an entity. And so we keep having schools reach out to us. We finally made trying to make a list of providers who will write these prescriptions, but there are a lot of roadblocks. You can just like everything we're talking about, but identifying them and then addressing them.

So another one is, you can have stock epi for daycares and schools now here and hopefully someday colleges, but one is to say, yes, we want the school to have it. Then the school has to take steps to get it. And even the epinephrine that is offered by the epic companies to give free to schools require a prescription right now. So getting access to a prescription every year from a physician isn't always easy for these schools. So we have a lot of schools even in Chicagoland without epinephrine because of that roadblock.

And then like everyone mentioned, once you get the epinephrine, then it's training and nurses, as we know, a lot of them used to like to keep it in the nurse's office and nurses, at least in Chicago, I shouldn't just play down Chicago so much, I might get in trouble, but love Chicago. But the school systems, there is a nurse there not every day, right? Usually maybe once a week if we're lucky. And so how do you train other staff to use epinephrine? And so those are some of the roadblocks we're seeing or we've experienced in schools.

And then colleges is a whole nother thing because we finally got epinephrine into a couple colleges that I know about that we work with, but there's a liability issue there too for the food distributors that work in colleges. They don't want the liability of having epinephrine in the dining halls. So getting past that too, so that, like you said, Linda and you work with them, and I have a college kid with food allergies, so

getting them to carry it is challenging. So if we could just have them in the dining halls, easy access would be ideal for that population as well.

Christopher Warren:

Yeah, that's so interesting because a lot of states have passed liability protection or good Samaritan laws for entities or individuals who administer epinephrine in good faith, but that does seem like a conspicuous gap where the person actually creating the situation where the epinephrine might be used to help someone in need still is potentially at high liability risk. So I don't know if there've been any policy efforts to try to address that state in different jurisdictions. I'm not aware of them, but that's a really important thing to flag.

Michael Pistiner:

So what's coming up is that there's incredible variation. So there's variation from state to state. Each state has different regs. Then even within different schools, so now thinking about elementary, middle, high school, you're going to have the different developmental ages, think about different weights, different thigh sizes, different noses. And so there's going to be different things that people need to be thinking when they're thinking about epinephrine. And so now, if you think this is a little bit tricky, K through 12, you're going to hyperventilate when you start thinking about preschool, because in preschool, it's like the wild west. And so let's kick it off to our team.

Kelly Cleary:

My mind is still in what you just said. So sorry to go back and the inconsistency. But one of the things that I know a lot of the advocacy groups are working on is the state legislation that allows for the stock epi within schools now that there are new modalities at a state by state level, all of those, that legislation needs to be changed to allow for new modalities to be present in school. So yet another roadblock where maybe as Ruchi said before, there may be companies where you can't get epinephrine, but in certain instances, the modality is dictated by legislation. So hard to do. But, back to daycare.

Michael Pistiner:

Wait, I'm going to go back to K through 12 now because now imagine a prescriber prescribes a form of epinephrine that that school cannot administer. Now, does that mean that family needs another round of epinephrine autoinjector specifically because school staff is trained on that? These are challenges that are going to be coming up as we spend more time on this. There have been states that have already rolled out and said epinephrine is epinephrine, but there are still some holdouts where auto-injectors are what unlicensed assistive personnel can be trained on. And so in this way, when they're asking for epinephrine to be put into those schools, they may reject something that would otherwise be fine for the kid. So this is going to be, we're all going to need to be working on this stuff and thinking about it.

Audience Member:

Can I make a comment? I'm not on this panel. But when it comes to epinephrine for a child who had the diagnosis and has an action plan, in all states, it is accepted that that child can have their prescribed device. When it comes to stock medication, states do have regulatory oversight as to what is permitted to be a stock device. And as for the liability protections, in most of the legislation, there is liability protection for the prescriber, the administrator, or the person administering it, the school, the entity. And then if people are interested in robust and agile legislation, Louisiana has taken school, K through 12 school entity and non-school entity and made very nice, very agile legislation that applies not just to

stock epinephrine, but also other emergency medications like albuterol, life naloxone, so that when another medication comes up that our schools or camps need, we don't have to go back and forth to the legislature. We can go to our Department of Health where it's locally regulated and more promptly get what our communities need.

Michael Pistiner:

All right, thank you.

Linda Herbert:

Can you reorient us?

Michael Pistiner:

Yeah. Going back to preschool. So now these are issues that have been now happening in K through 12 schools. And another thing to also keep in mind is in many K through 12 schools, there's school health, there's school nurses. The school nurses could train, the school nurses work on policy, the school nurses collect paperwork. And now in preschool setting, this is my kind of humorous mention of the wild west is there's less consistent communication and school health services in many cases is not a thing. So with that.

Linda Herbert:

And that is coupled with high turnover. So we might not see the same rate of turnover in first grade class or fourth grade class as we see in preschools. So there's just parents report a lot of continued need to educate and provide information as there is this turnover. And there's certainly a high element of fear among parents, among many parents who have kids in preschool or daycare, just because their child cannot tell anybody that they're experiencing symptoms of allergic reaction. We might have a couple clue words we might hear like, I throw it as spicy, itchy, there's like hot, there's words they might use, but there's a lot of reliance on adults to know exactly what they're even looking for in order to know when to provide treatment.

Kelly Cleary:

And add to that, the developmental stage within preschool. So there was a study years back that looked at kids two to five, put their hands in their mouths 40 times a minute, and those under one, it doubles to almost 80 times a minute.

Michael Pistiner:

An hour.

Kelly Cleary:

[inaudible 03:46:08] Oh, it's an hour. It's an hour. I'm having time issues. 100 times in an hour. It's still significant. So that's another layer that someone who is governing that class needs to take into account that these kids are putting their hands in their mouths all of the time, touching one another, not knowing boundaries, not knowing about their food allergies. And then on top of that, not being able to communicate that food allergy.

At FARE, we do a bunch of teaching to daycares in particular. And when they're local, I'd love to go on site to see some of the schools. And I have to say that those providers are often the ones that are most

fearful of these kids coming in and want the most amount of direction because they don't have any governance within that. And when they speak about epinephrine coming into the school and in some communities, the family is not able to provide a second pack of epinephrine to the school because of affordability. So I think that preschool, it's developmental, it's high turnover, but it's also just, it's unregulated and not consistent.

Michael Pistiner:

The legislation also is a bit different. So in the K through 12 setting where all states by Hawaii have stock that is worked in there, that's not the case in preschool daycare environment. So there are going to be some states where the unknown first time allergic reaction and think of potential babies with feeding new foods may then be exposed to have an allergic reaction, and there isn't stock epinephrine available. Now also then And think about the size. So now if it happens to be a six month old, 7.5 kilo kid, then it's going to be things to be thinking about. It's going to be the form of epinephrine that would be appropriate to be there.

The other thing that we're not even talking about when we mentioned K through 12 and now preschool is that in the case of stock and in the case of the child specific epinephrine, we have expiration dates. Think about the amount of epinephrine that is just getting tossed from the shoe racks that are hanging on every school nurse's door.

Ruchi Gupta:

Yeah. I was going to also ... Yeah, we use all that epinephrine for those trainers when we have people work with the grapefruits, which is a really great use of them if anyone has hundreds of expired ones sitting in their closet like I do.

But just back on preschool, because I think it's so important. We did a whole study in preschools and one in four preschool staff have observed an reaction in a child. So it is common in everything that Kelly and Linda and Mike, you said, but also these kids are often trying foods for the first time. They haven't had so many of these foods, they're infants or toddlers. And so they're not only putting their fingers everywhere, but they're sharing foods. So it is so critical for the staff in childcare centers to be well trained and understand how to recognize a reaction and have epinephrine available, stocked because many of these kids may never have had a reaction and are not dropping off epinephrine to their schools.

Also, what's come up a lot for us since we do all this work in prevention is parents who want to send the foods, peanuts or peanut products to childcare centers for them to feed to their child and it's banned there. So there's a lot of different areas that have started coming up in childcare centers, but I think that is probably the most important place to have stock epinephrine available and very well trained staff. And Elijah's Law started this and it's going across the country, hopefully just like in schools soon enough.

Michael Pistiner:

All right. Now let's take to the big kids. Let's talk college.

Kelly Cleary:

I think that's preschool certainly is an important time, but I think college is too. I think that's oftentimes where we're hearing from patients, it's the first time they've had to navigate. I've had patients who are writing in and we're calling them back and they're treating themselves alone in their room and calling their parent. So having stock epinephrine or having more training for resident advisors. And also from college to college, the policy is very different on who responds-

PART 7 OF 10 ENDS [03:51:04]

Kelly Cleary:

College to college, the policy is very different on who responds if you call for an emergency and whether or not they're taking you to a hospital or they're treating you here and they're taking you to a medical center. So really knowing that part of college, but it's also risk-taking. We see drinking and unfortunately drugs that may impair decision-making and may also lower that threshold for anaphylaxis. So I think that it's an equally important time to think about having epinephrine more widely available just given that age and stage.

Linda Herbert:

I cannot agree more. And I think any place outside of the home having epinephrine available in a stock format is so valuable. Before you even get to carrying epi, there's decisions that you're making about food safety. How are you deciding what is okay to eat and what is not? And especially during this adolescent age and into college, what I hear over and over and is, "I know what to stay away from. I know what I can eat. I've eaten at that restaurant before. It's fine. Oh, if I really need it, someone's going to have epi." The patients that terrify me the most are my college students who won't carry epi because they say someone will have it. And I'm like, "Okay, take deep breaths. I can only do so much motivational interviewing in 15 minutes."

But it stresses me out. And I really just think that there's a lot of assumptions about safety that are being made. And we cannot ... I'm only one psychologist. I can only do so much to try to change some of these assumptions, but we need to be really aware that people are making these assumptions and provide this extra kind of blanket of protection to help while it's really this top down, bottom up approach. We want to educate, we want to really work on that health behavior change. And at the same time, ensure that we have a social network that is providing that extra care in the moment that it's needed.

Kelly Cleary:

And developmentally, they have the ability to give those words of, "I have a food allergy," but we're hearing that they're not. Because of the stigma that you mentioned before, one of the campaigns that we're doing is speak up, let people know that you have a food allergy, because we hear about some kids who will be out to dinner with friends from college, and sometimes they'll just choose not to eat or to just sit there because they don't want to disclose that. So I think even with this age and stage, they have the words, but don't use them sometimes.

Charity Luiskutty:

Yeah, at the stage passing that responsibility onto them, training them properly. I think a lot of times they might underplay what is going on when there is a reaction, carrying the epinephrine, treating promptly. But being on college boards and such, it's obvious that universities and colleges don't have their ... You talk about the preschools being the wild west. It seems like colleges are that way too as far as policies and procedures. If a reaction occurs, how is that taken care of? Do you call security? Security doesn't have procedures in place as to what they're going to do. I mean, some may, but it's all over the place. Or do the students call 911? Or often they may not even activate anything. They'll go off by themselves. So yeah, I think there is a big gap in how things are handled at that level.

Matthew Greenhawt:

Being available.

Linda Herbert:

What comes to mind for me is places that we have AED's. People are now familiar with seeing AED's and easy to use signage and automated voices, that type of thing. And so that's what comes to mind for me now as far as people recognizing where to find those or signage. So I think now that that's commonplace, that's what I envision for EPIPENs or epinephrine devices.

Ruchi Gupta:

Yay, we're back. Hi. I don't know everything we missed. I have an old statement, so maybe it's not relevant anymore. I was going to just mention going back to college just a little bit, just real quick, just because we have some data. Half of kids in colleges with food allergies have had a reaction in college or say they have. And also, a lot of kids who go to college don't even tell the college they have a food allergy. There's not really a formal way like preschool or there are forms, but they don't notify them or get them a doctor's note many, many times. In fact, I'll divulge. But even when my daughter went to college, even knowing everything I know, I didn't actually formally give the school something in writing, which I think is something as physicians, we need to make sure our patients are doing.

And then I have to give a shout out because I guess this is a Duke event, but Duke is doing an amazing job and has stock in their dining halls. And so does a lot of schools, Michigan, Northwestern. I think we're getting more and more, but it is not common to place. And we need to have the epi manufacturers help support us to get them into these colleges. And then I know I'll transition. You guys were talking about AED's and putting epinephrine in there. Is that an EMS? And that's all inconsistent too in a state by state because some have epinephrine auto injectors, some have vials, some have nothing. In the first week at Northwestern, I think six kids had to go to the emergency room for a food allergic reaction because kind of like what you guys said, they're all trying new foods and going to parties. And what is it? Indestructible or nothing can hurt them. So I'll stop there because you guys moved on.

Christopher Warren:

And data suggests only about one in five of these college kids are routinely carrying their epinephrine all the time. So the need for undesignated is even greater in that context for sure.

Matthew Greenhawt:

And now on top of things, we also have these kids who are now transitioning from pediatric to adult care. And so there's a little bit less handholding sometimes once you get to an adult clinician.

Ruchi Gupta:

That's right.

Linda Herbert:

If you get to an adult clinician.

Kelly Cleary:

Yep.

Matthew Greenhawt:

[inaudible 03:57:36] that's good. All right. So now we've talked about public places. You guys feel like we hit upon eating establishments arenas enough. One of the things that we don't want to do is send a message that people don't need to have their own epinephrine. So we don't want people to think you could just go out and you're wearing tight fitting clothing so you're not going to carry your epinephrine. So you're going to go to the game and you'll be fine. We want people to continue to carry their own, that this is a backup plan and this is for people with unknown and for people who perhaps forgot, but we still want to reinforce to people that they need to be carrying their own EPIPENs.

Linda Herbert:

Yeah, I completely agree. And I think that's where this bottom up, top down approach is just so important is just empowering patients to do what is best for them is key. But since we know that there are so many individuals who aren't getting adult care, who aren't seeing an allergist, we have to have these other layers that really help out.

Matthew Greenhawt:

And then when oh, I'm sorry.

Kelly Cleary:

Oh, no, I was just going to say, and outside of K through 12, I think Ruchi brought it up earlier, but in public venues with the thought of having stock epi, it also with liability. And we hear that often that people are concerned that, again, that is something that varies often from state to state. And I think that that is something that we have to be thinking of to allow people to feel like they are empowered to use the epi if it's there without consequence.

Matthew Greenhawt:

And then to add complexity to that, is it about just the epinephrine being there or then is someone going to be trained to administer that epinephrine to someone who perhaps is unknown? That adds a more challenging effect. And when we're thinking about K through 12, many schools have administrators or school health who are good at that, where then you now think about a restaurant. Then are restaurant employees going to be up to being able to recognize first time allergic reaction [inaudible 03:59:54]. Shall we move to airplanes?

Ruchi Gupta:

Yeah, just one thing, CPS was really worried about that. Will people bring it to school on their own? And they put posters up and the motto was, "We're prepared, are you?" So trying to get ... We're doing our job, you do yours. You carry your own epinephrine and make sure you've got your action plan. So I think there are ways, but yes, airplanes. I may turn that over to Chris.

Christopher Warren:

Just go? Yeah. Well, I think we're in a ... It's the thunderdome after all, right? So one thing that I'm actually excited to have just realized is that every single member of the panel all collaborated in some form on a study of food, allergy and air travel that we conducted a couple years ago. Ruchi and Linda and I developed a survey that then was administered to about through 50 different organizations, in fact and FAIR were among them. And it was intended to provide some additional data beyond the paper that Kelly cited earlier, just looking at experiences that food allergy patients were having with air travel.

And one universal is just that air travel is an anxiety provoking environment due to a lot of reasons. But one factor has to do obviously with what happens if you have a reaction. And even if in a best case scenario where you're carrying epinephrine and you know what to do and you know how to recognize a reaction, what's going to happen. There's a lot of uncertainty there.

But to the point around epinephrine. Access, which is I think where we're really targeted here, one of the things we found in our survey, which targeted about 5,000 patients was that a little over eight, about 8.5% of patients reported that they had had an allergic reaction in the sky. And almost all of those events were treated with the patient's own epinephrine. And so this has implications because when we try to figure out using administrative data, how frequently reactions are happening so that in FAA reauthorization and such, folks can make data informed decisions about, "Oh, what's the real risk of having a reaction in the sky? What are the real outcomes?" Simply that those data are not routinely being collected. In our survey, about 40% of patients who had a reaction in the sky did not report that either to the airline or ground EMS upon landing.

And then if the FAA or if the emergency medical kit's not cracked, that's not tracked either. So we just don't really have good visibility into what these rates are. Of course, our survey was a convenience sample to a certain extent, but I do think the issue of it's timely to bring this up now and really maybe have a discussion about what should be in those emergency medical kits because it's required that vials of allergy dosage epinephrine be in there, but there's certainly been plenty of anecdotal reports and well investigated reports where when those bags are cracked, there's no epinephrine in there or the epinephrine's certainly not in an easy to use format.

And now with neffy being approved and it looks like NARCAN's going to be put on in those emergency medical kits likely with a lot, frankly, less data than exists currently for the ubiquity of reactions in the sky. I think to me it does raise issues of whether or not we should consider more user-friendly formats of epinephrine being present in those kits and it truly being mandated. So just a thought.

Matthew Greenhawt:

The final setting for us is going to be the healthcare setting where you have allergy teams during oral food challenges, you have primary care giving vaccines, and sometimes families just showing up with a kid in an allergic reaction. And then also thinking about code carts. So the form of epinephrine that's available and the different ages and sizes of patients to be thinking about, these are just other things to think about when it comes to epinephrine.

Linda Herbert:

One thing I think is interesting about the oral food challenge setting is that there's also inconsistency across institutions as to whether or not you can treat an allergic reaction during the food challenge with the person's own personal epinephrine auto-injector device or an auto-injector in general. I know at my own institute, we've gone back and forth. We traditionally have had to use a syringe. For a brief amount of time, we were able to use EPIPENs and families liked that. They liked seeing how it worked, having that experience. We had teens self-inject. I think it was incredibly educational and empowering. And then we were told we're not allowed to do that anymore. So now we're back to our original system. And I think there's really a lost opportunity there. And I don't know what happens at your institute, but my understanding is that there is a lot of variability across.

Matthew Greenhawt:

Some of our providers use the family's auto-injector or our own auto-injector depending on the age of the kit. We had a study where we had parents administering after they were trained, and in general,

they were having a positive experience even though their kid had an allergic reaction that required epinephrine. And what we heard in qualitative study afterwards was that they felt empowered that they saw their kid feel better quickly and they were actually able to do it. And then looking forward that they felt that they would be able to do this in a community setting. And so that's utilization of epinephrine, community accessible epinephrine during those cases really can be helpful.

Charity Luiskutty:

We use syringes and auto-injectors. We can choose, we offer the patients if they want to use auto-injectors. Most do not. But like you had mentioned during oral food challenges or oral immunotherapy, almost always it's a positive experience for the patients and the caregivers that they walk away with seeing how quickly it works and they do feel more empowered. And I think it's most beneficial to see the ... Well, we use the auto-injector and we were a part of the real-world use for neffy as well, but for the patients seeing how to use devices or products that they could use in real life, that it's an empowering situation for them.

Matthew Greenhawt:

All right. Just to give you all the chance to keep coming at us, any barriers to access that we haven't hit upon in our session just anything that you think we missed?

Carla Davis:

So I just didn't hear about the variability that may exist from lack of funding. So I know that in Texas when stock Epi was rolled out, the schools and the individual entities were given the responsibility of paying for it. And so those schools, private schools that had motivated and parents with resources were able to get it. And so my question, if we could just talk about the economic impact and potential contribution to the variability that may be due to the economics and resources.

Linda Herbert:

Well, I mean, I think what you're pointing out is the stacked set of health inequities because it's also likely that the individuals at those schools might have greater access and resource to epinephrine auto-injector anyway. So we really have a compounding impact. And I don't have an answer to that, but just pointing out this really is stacking up for families.

Kelly Cleary:

I don't have an answer either, sorry, but what we do hear that often, and then that there are in the epinephrine for schools programs, the lags in schools actually receiving them and then trying to look for ways in which they could pay for, and that's where we hear from families who are concerned that their school doesn't have stuff or the nurses calling us and asking, "How do other communities do this?" So a hundred percent, you are right, probably in the communities where stock epi would be needed so much often with delays in getting those from the community programs that they're not having it because of cost.

Ruchi Gupta:

I can try to answer that, Carla. I feel like what we've seen is if a whole school system buys it, it's definitely expensive. I know when we did it in Chicago, they take bids from epi manufacturers and try to get the best bid and then put it into the schools. Now, I know a lot of the epi manufacturers have programs where they give schools free epinephrine, stock epinephrine, but then again, it's the

awareness of those programs and getting someone in the school to apply for it and get the prescription, et cetera. So I guess my answer is you're 100% right.

There's so many disparities and exactly what Linda and Kelly said, stacked on in different ways, but the programs exist. If we can somehow get the states to at least let the schools know that they have an opportunity to get free epi, really appreciate manufacturers doing that. There are ways that they can get it in the school. It's just, again, awareness, education, and then additional state funding if needed.

Christopher Warren:

Yeah. And another thing that just coming to mind is, I know there have been some efforts to try to understand what's the cost effectiveness of epinephrine in different contexts at different price points. And if we're dealing with a publicly insured pediatric population, which you are predominantly in many public schools, it would be interesting to do a study to try to understand if by administering epinephrine earlier in the reaction to the point where it's not advisable to go then to utilize emergency medical services, go to the ED, which we all know is costly, could this actually be cost-effective for the payer who's either paying for it on the front end or the back end? Just something to think about because I think increasingly we just need to think about how to make these interventions cost-effective and in different scenarios.

Matthew Greenhawt:

That's actually relatively well modeled, Chris.

Christopher Warren:

Yeah. Well, and you're talking about this next, right?

Ruchi Gupta:

Yeah. [inaudible 04:11:49].

Christopher Warren:

I'll set them up, you knock them down, Matt.

Matthew Greenhawt:

Saw a hand.

Paul Greenberger:

Paul Greenberger again, I would point out that when public good, you're looking out for it, you need to get legislator assistance for the net good. We left that off with who were the stakeholders this morning. Was not intentional, but we need to make collective effort, contact legislators who could make a difference. In Illinois, Senator Durbin, who has been in the office a long time, years ago, sat down with the airlines who didn't want to have smoke-free areas on planes because they feared people wouldn't fly if they couldn't smoke. He was able to put enough pressure on them, I think threatening legislation or whatever, put enough pressure to ... I think for a while they had three rows where there could be smokers, and then I think it's all gone now. So the talent in this room needs to come forth and identify legislators who should be sitting at the table to help us improve access. At least that's my opinion.

Matthew Greenhawt:

All right. The last question we've been tasked for is in each of our opinions, what is the most exciting opportunity in [inaudible 04:13:24] for access?

Linda Herbert:

That's a big question.

Matthew Greenhawt:

That's a big one. I'll start. I think that having epinephrine available at the time of discharge in the emergency department, along with action plans and initial training, I think that that really could go a long way.

Kelly Cleary:

I'm going to mess this up, Matt, but I can't pick one. I think that expanding access to epi and expanding family's ability to afford epi and teaching, whether it's schools or families that epinephrine and anaphylaxis is not the last resort, but is the first line. I think that all of those things excite me. So sorry, I can't pick one.

Matthew Greenhawt:

Made me regret mine.

Charity Luiskutty:

I would have to say expanding affordability and accessibility to patients because without that, we can't even get in the hands of them. And then education with the patients and the reinforcing early epi and getting comfortable with the use of it. Those are the big things that I'm excited about and look forward to progressing.

Linda Herbert:

I think for me, there are two things. One is just patient choice. So having options because we know that how you feel about your medication really dictates a lot about whether or not you use it. But the other thing is just opportunity for public education, because the more that the public is aware, the better for everyone. And with greater public education, we also then might be starting to tackle the stigma piece as well, which is a huge factor.

Ruchi Gupta:

Okay. I'll go and then Chris, you can have the last word, first word, last word. Okay. So I agree with what everyone said. I have to say, in 20 years of being in this space, we have come such a long way with epi, and that in itself gets me so excited. We had one option, didn't know much about it, and now we have multiple options, and hopefully that means letting patients choose and giving them the option that they want in their hands. And I'm really grateful for what is happening today there, because all this awareness and education and thought leaders in a room is definitely going to make an impact in the areas everyone mentioned, awareness, education, access to all our patients and all, not even patients, people who have food allergies and can't get to a doctor, getting them education and access in all open spaces. So this is awesome. Thank you so much for doing it.

Christopher Warren:

Yeah. I mean, just to build on what everybody said, and Linda's comments really resonated with me and Ruchi summed it up nicely, but I do think just the idea that we're moving more towards considering epinephrine as a public good, almost like a right in certain contexts that people deserve because such a substantial proportion of the population is at potentially at risk of anaphylaxis is really heartening and the potential of that to normalize carriage, normalize having allergies, and just generally reduce the burden that a lot of families and patients live with every day in the context of more choices that can help keep that virtuous cycle spinning around.

And the state level caps on copays, I think is another promising development, just that there are a lot of forces working to try to get epinephrine in the hands and buy bodies of people who need it. So thanks for hosting this.

Matthew Greenhawt:

All right. We'll wrap things up. Thank you so much for having us. Go team.

Julie Wang:

All right. Welcome back everyone. [inaudible 04:17:31] and I'll be moderating just that last session. The title of the session is Opportunity to Enhance Access to and Use of Epinephrine. So we've talked about barriers already. Next session will be more forward, thinking what [inaudible 04:17:48] can we make. I think that for me I'm thinking feasible things, but also I think we should also be a bit more creative and things out of the box that maybe are not quite useful right now, but potentially could be possible in not too distant future. So in this discussion, we'll have a chance to bring all everything together end of day and then really impact would be made going forward. We welcome audience members, both virtual and in the room, submit via the Slido app. Any further questions and your thoughts on the most important opportunity to enhance [inaudible 04:18:28].

So I'm going to introduce our esteemed panelists, and then we'll begin with opening remarks from each of them. Our panelists are Tim Dribin, Associate Professor of Pediatric Emergency Medicine at Cincinnati Children's Hospital Medical Center. Matt Greenhawt, Chief Medical Officer for the Asthma and Allergy Foundation of America. Nissa Shaffi, Director of Advocacy at the Allergy and Asthma Network. And joining us virtually will be Marcus Shaker, Professor of Pediatrics and of Medicine at the Dartmouth Guidell School of Medicine and a member of the American Academy of Allergy, Asthma, and Immunology Board of Directors. So I'm going to ask each of our panelists to give a three minute or less opening thoughts on opportunities. And we're going to start with Tim.

Timothy Dribin:

Well, thank you very much for having me. This is a really important meeting and I think it's going to accomplish a lot. Thank you very much for all of the organizers. I'm a pediatric emergency medicine physician and beyond trying to optimize how we manage patients with anaphylaxis in the emergency department and when they go home, one of my key research areas is trying to improve the recognition and management of anaphylaxis and acute allergic reactions in the community setting.

So as a little bit of background, I always, before we try to look at how patients, caregivers, lay people are managing anaphylaxis, I always try to first look at how do we as healthcare professionals manage this? And a lot of times we, I think, try to say, "Oh, we all manage this the same. We recognize it the same." But even from the first session this morning, we were asked, "Would you give epinephrine if someone had hives on their chest?" Or, "How many hives would you give epinephrine?" I think what we recognize is when you ask people, clinicians, there's a lot of variation when they decide to administer epinephrine.

If I ask my colleagues in the UK, in Germany, Australia, they have a higher threshold. They're like, "Oh, we don't give it unless there's airway breathing or cardiovascular problem. You Americans are giving it for all these more mild symptoms." There's a great study that Julia was a part of, Mike as well, and then Carlos Camargo and Jay Lieberman where they asked pediatricians in the US and they said, "First, do you think someone's having anaphylaxis? And then second, would you give epinephrine?" There was quite a bit of discordance among those responses. So even with healthcare professionals, there's a lot of variation.

So I think the point of that is to say that the variation in healthcare professionals, then I think it makes sense why there's so much variation under use of epinephrine by patients and caregivers. And I think one of the most challenging things is that it's a multi-system organ involvement. So managing asthma is challenging, but usually the presenting symptom is trouble breathing. But with anaphylaxis, we're asking people to recognize respiratory involvement, cardiovascular involvement, gastrointestinal involvement, skin and mucosal involvement all at the same time.

And the second component of that is that reactives are very dynamic. So patients can be mild and do fine, then all of a sudden they can get much sicker. So we're having to train people to reassess and to make decisions about do we need to give epinephrine and do we need to re-dose epinephrine? So we're asking people to all of a sudden become healthcare professionals who are trained in advanced cardiopulmonary resuscitation, which is incredibly challenging. So one of my big research areas is to say I think access to epinephrine is critical, but we need to try to have resources and technology to support patients and caregivers in recognizing when to give epinephrine and then making sure that those patients who have [inaudible 04:21:53] are the most life-threatening presentations, their repeat doses of epinephrine that activate emergency medical services.

So one of the big studies that just came out in Journal of [inaudible 04:22:04] Clinical this past week is we convened 34 member international anaphylaxis panel. And also we had 19 patients and caregivers from around the US, Canada, and Australia. And our first task was to say, "Can we develop consensus recommendations for when to give epinephrine?" We developed 24 clinical scenarios that spanned different anaphylaxis organ systems. And of those 24 clinical scenarios, epinephrine was recommended for 21 of those. Two scenarios experts recommended not giving epinephrine. And then for one scenario, there wasn't consensus. The other part of this study was to try to figure out, can we have consensus recommendations for when to go to the emergency department and when can you stay at home? And there were 10 criteria that experts recommended activating EMS.

So if you can imagine, we have 24 clinical scenarios for when to give epinephrine. We have 10 scenarios for when you should go to the emergency department, and that's a lot for people to integrate into real-time decision-making. So the future right now that we have these algorithms is we're going to develop a smartphone application that'll be free, open access that patients and caregivers can download, that they input their symptoms and provide real-time prescriptive treatment advice because patients and caregivers have told us through these interviews that they want to be told, "Should I give it? Yes or no?" That they are uncertain, that they lack confidence, that they want to receive real-time advice about when to give epinephrine and to take that uncertainty away from it. So hopefully that's an opportunity to, once we have more devices out there to improve recognition and treatment.

Julie Wang:

Thanks, Tim. All right. Next, I'm going to give Marcus a couple minutes to share thoughts and opportunities.

Marcus Shaker:

Oh, thanks, Julie. Did you see me?

Julie Wang:

Yeah.

Marcus Shaker:

Great. Thanks. Thanks to the organizers for the opportunity to join. And my goodness, what a fantastic session. So there's a story of a little girl walking on a beach. Carlos heard this story, and the beach is covered in starfish. And so she knows ...

PART 8 OF 10 ENDS [04:24:04]

Marcus Shaker:

And the beach is covered in starfish. And so she knows the starfish aren't going to survive unless they get to the water. So she starts putting the starfish in the water. And this older gentleman walks up to her, the crowd's gathered to see what she's doing. The whole beach is covered in starfish. And he says, "Little girl, what you're doing isn't going to matter. This whole beach is covered in starfish. You're never going to get all these starfish in the water." So she looks at the old man and she thinks for a minute, she takes the starfish and she throws it in the water and she looks back at him and she says, "It mattered for that one." And then the story goes that everybody kind of joins her on the beach and puts a starfish in the water. The reason I mentioned this story is that's what we're doing here.

We are standing by the good and we're making it better. And I am grateful to the organizers of Duke-Margolis, to our colleagues and regulatory positions and to the innovative work that's been done by the developers of non-injectable epinephrine, which has been a tremendous innovation. Because when you think about the data that less than 25% of kids get community epinephrine, less than 10% of adults who are having anaphylaxis get community epinephrine. And you say, "Why?" Well, I mean, it's not a monolith. And for a lot of folks, they're afraid of the needle form. For a lot of folks, they don't have access to it. As Dr. Davis mentioned earlier, for a lot of folks, there are pharmacoequity issues. I have patients who I prescribe epinephrine to and they come back and they don't have it for all of these reasons.

So the challenge to us is how do we continue to encourage innovation while at the same time creating an equitable environment that's honest and fair? How do we remove the barriers? The question is not, should epinephrine be over the counter? It already is. It already is in a dose that's 10 times the dose that you see in the nasal epinephrine inhaler. You can go to the pharmacy after this session and for $30, buy yourself 20 milligrams of epinephrine and a Primatene mist. The question is, how do we create access to epinephrine in forms that are appropriate and how do we create guardrails? If a pharmacist is able to give a vaccine, is a pharmacist able to teach how to do nasal epinephrine? So really, it's been really interesting to hear everybody's perspective. I'm really interested to hear what my fellow panel members think. Thanks, Julie.

Julie Wang:

Thanks, Marcus. All right. Going to turn it over to Matthew.

Matthew Greenhawt:

Thank you. Thank you to the organizers for inviting me and for allowing the Asthma and Allergy Foundation to participate in this. I'm going to lean in a different way, which probably won't surprise many of you who know me. So there are all kinds of barriers, and I'll say this. One, the barrier is, so it's more than just food. We need to keep that perspective that there are broad causes of anaphylaxis while food might be the most important trigger for most of us in this room. It goes far beyond that. And for the food allergy community, their needs are met, but things like venom and drug allergy, they lag behind a lot and we need to keep that in perspective. So you think about barriers and whatnot. So you could look at these as procedural things, policy things, regulatory things, and those that we self-impose. And maybe the self-imposed ones are the ones that are the most uncomfortable to talk about.

The thing that's my specialty is making people uncomfortable with uncomfortable points, but we need to look within ourselves and what we're doing as allergists. Access to epinephrine maybe isn't the biggest issue to address. I think it's pretty easy to get epinephrine if you really want it, as long as we have insurance. There's somebody out there with even just a half backed story who generally will prescribe it to you. It might not be the form that you want. You might have limited choices. But our issue is getting the people who have it prescribed to them to either pick it up and or use it and carry it with them. And until we fix that, putting more epinephrine into the system isn't really going to help. So why are we lagging behind? Well, one, we have a misguided focus. We focus on mortality as opposed to morbidity.

Mortality from anaphylaxis, it is very, very hard to die for anaphylaxis. So that makes people uncomfortable to hear. I urge you to go and look at all of the data. It's a compounded effect. Usually two, three things in a Swiss cheese model have to happen. Epinephrine works and survivorship without epinephrine is actually quite common. I encourage you to go look at the European anaphylaxis data registry to see how many cases with severe anaphylaxis do survive without epinephrine. So if we focus on morbidity, now we can back it up. Our evidence and our guidelines really are poor and we don't have good studies because it's hard to study anaphylaxis other than observational or single arm studies or whatnot. You can't do randomized control trials. So let's work backwards. What's the problem? Nobody wants to spend 48 hours in the emergency room. They've got a lot better things to do.

So that sits in their mind. And if you don't want to do that, then certainly you're not going to call EMS because you don't want to sit in the emergency room. And as Brian said this morning, maybe you don't want to use a device that's expensive to refill and maybe you don't want to have to carry two or four or how many ever your action plans says to always have with you at all times. And if you're uncomfortable giving yourself an injection, how do you think a layperson who's never seen you before might feel in treating you or your child or something like that? So we need to get out of our own ways sometimes. And I think our policies have been backwards. Now Mark and I have spent a better part in the last eight years disrupting how we think about anaphylaxis care from a cost-effectiveness standpoint. Most of what we do doesn't have value, mainly because it's geared towards preventing mortality, which is, again, it's too rare to predict.

If you start thinking about the morbidity, that's a little bit easier. But why keep somebody in the emergency room for four hours? If you're stable after an hour, there's a 95% negative predictive value that you will be fine. Start from there. But we make these rules. Can we predict who's going to have biphasic anaphylaxis? There's going to be data coming out on that. The EMS, there's no value in that. You have to have a 500-fold increase in fatality, which is implausible. And then you need to get care 75% of the time that you hit the emergency room with that risk. It just doesn't add up. So we as clinicians maybe need to let go. And if our policies are a little bit easier to follow and adhere, maybe the patients will have a little bit of easier time wanting to take whatever form of epinephrine. Now add into that that we have choices, we're making it better. If people don't want to inject, then don't prescribe them

something that they have to inject. Think about that in terms of what we can do to maybe change the paradigm.

Julie Wang:

Thanks, Matt.

Nissa Shaffi:

Hi, everyone. Hello?

Julie Wang:

Yeah. You're good, yeah.

Nissa Shaffi:

Hi, I'm Nissa Shaffi. I'm director of Advocacy with Allergy and Asthma Network. We thank the Duke-Margolis Institute for Policy and the FDA for this convening today and for the opportunity to weigh in on such an important conversation. If you're not familiar with the Allergy and Asthma Network, I'd love to just briefly touch on some of our priorities and why it's such a privilege for me to be part of this discussion because a lot of what was discussed today ties in very beautifully into what we're already working on in the legislative and regulatory space. So at the Allergy and Asthma Network, through our patient-centered research, our federal and state advocacy, our educational programming and our outreach efforts, we help to improve the lives of all individuals impacted by asthma and allergies and related conditions. And we have been doing so for 40 years.

And our goal is to help advocate for policies that reduce life-threatening emergencies. We work to advocate for federal funding. I remember a question earlier about funding at the state and federal level for allergy and asthma programs. We try to mitigate environmental hazards. And of course, pertinent to today's discussion, we work on affordable access to treatment. So a couple of things I want to touch on is the fact that there are so many legislative proposals that currently tie in to today's discussion. Most of them focus on upstream solutions, emergency medical solutions, as well as community-driven solutions in the legislative space. So working on affordability of these services to patients, making sure patients can access them at a price point that makes sense to them and is feasible. Making sure that there are good Samaritan protection laws in place so that those individuals that are involved in these crisis responses are held harmless in these emergency situations, as well as training and resources to law enforcement and first responders, which we've heard throughout the course of today's discussions.

I also want to touch on some of the stats that we heard earlier. Thank you to Dr. Sampson for showing Allergy and Asthma Network's infographic. So one in 20 individuals have experienced anaphylaxis out of which 51% of adults and 42% of children present severe allergy symptoms or reaction, sorry. Anaphylaxis results in over 225 deaths per year and costs about a billion dollars annually to the United States healthcare system. So these are some of the societal and economic impacts that this condition present. And epinephrine, as we've known and have learned today, is the first line of treatment for anaphylaxis making its timely and actionable administration incredibly critical. However, we've listed a lot of the barriers that are present in this space, and a lot of these were already touched on making sure that state laws are moving in lockstep with medical innovation. So there are currently 49 states that are permissive of allowing stock epinephrine. There are 10 states, including the District of Columbia that require, sorry, mandate epinephrine stalking in schools.

And only five states that allow for FDA-approved delivery devices. We need to make sure that the 10 states and the 49 states that only allow for auto-injectors that are stocked move in tandem with FDA-

approved products and that these laws are cohesive and comprehensive across the board throughout the country. And the last thing I want to touch on is I know that we've been discussing regulatory proposals like OTC, RFIs that the FDA has issued. There's some health plan contingencies that I wanted to touch on, and that is the pros and cons of having a OTC epinephrine product. One is the availability and access presented to individuals who are bound to lose their health coverage in the coming weeks in Medicaid and the ACA. And the other is some cons related to individuals that do have insurance, but will probably face a lengthy reimbursement process in trying to get those treatments covered. But both situations called for effective cost analyses for what this will cost patients as well as proper training. So I'm incredibly here to be part of this conversation. Thanks so much, and I think I went over.

Julie Wang:

All right. Thank you, Nissa. So we're going to open it up to the panelists to discuss important categories. We'll continue the policy regulatory legislative potential opportunities, so I'm going to turn it over to the panelists to do that in a second. But then there's another category that I want to touch upon is new technologies. Can you mention one, whether there are other opportunities to do so, and there are some in the works, and then next step research needs, what questions do we need to answer? Where does research go to address anaphylaxis, epinephrine, et cetera? So to continue the policy and regulatory legislative topic, I'm going to ask Mark and Matt, if anyone wants to jump in about thoughts on additional, he's already shared the good work that you're doing right now, but are there other areas that we should be thinking about?

Marcus Shaker:

Well, one thing we tackled, and I think Matt might talk more about it too, is this idea of does every package need to come with two devices? So you talk about reducing the cost. One way to reduce the cost is to realize that it's the minority of patients that need a second device. If you were going to have an over-the-counter device, you have non-injectable epinephrine that's available in a single device. If you sold that for about the same price as what's currently available with primatene, you could sell it for close to 40 to $50. And if somebody was buying two, it would be under dollars, but they'd be able to buy that single. So there might be some different pricing models that could be used. I also think we need to be aware of if we are talking about over-the-counter models for anaphylaxis.

And it should be clear that the current device that's available is approved for asthma, and it may not be the most appropriate for asthma, any allergy. Well, Matt and I did a cost-effectiveness analysis on that, showed over-the-counter epinephrine actually led to increased rates of fatalities in the hospitalizations compared to an over-the-counter model of an ICS LABA. But regardless, it is over-the-counter right now. And so if we talked about an over-the-counter epinephrine for anaphylaxis, we'd need to be aware of how does that impact future innovation? How does that impact recent innovation? And how does that impact folks who are currently getting epinephrine for pennies on the dollar through their insurance, and would that still be covered? So those are all very real considerations that we need to keep in mind. Matt, do you have other thoughts on that?

Matthew Greenhawt:

No, I mean, there's a sweet spot where if the FDA is serious about making this over-the-counter, where it can be priced at a level where people just aren't hoarding it and buying too much and there's a disincentive, but it's reasonable enough that you can get it and that people who do get a nice discount on the deductible or whatnot, that there is a sweet spot where it also doesn't crimp innovation. And these new technologies coming out, needle-free forms, are going to revolutionize how we take care of

patients with anaphylaxis. There isn't a person in this room who hasn't nodded that there's a problem. People do not want to necessarily inject, so they need an alternative, but if we strip them down to where they can't make any money, then they're not going to put any new technology into the system. So there is that sweet spot.

But going back, we need to look at, again, the policy. Why is everything in a twin pack? Well, there was that little girl who died across the river about 13 years ago now, and she couldn't afford back when you could get a single pack. But somehow that went from having two devices to now two twin packs, but then you need two twin packs for school and you need this. And a lot of the things that we pat ourselves on the back for really haven't necessarily moved the needle. Stock laws are great, but if you couldn't afford the epinephrine to begin with, like she couldn't in a state where you have to supply your own because the stock can really only be used by somebody who's having their index reaction. And I do challenge that 25% statistic. That's from 2007, and that's never been replicated.

But fine, there's a small incidence of index reactions that happen. That's the only person who's benefited by stock right now. If you look at the model that Mark and I published in 2018 or 19 or something like that, if you went through universal model where you just put four devices, four forms, whatever you want to call it, in the Chicago public school system, you would save about $7,400 per child and there are about 300,000, 350,000 students in Chicago public schools alone. You can start doing the math at how much money we are wasting by having 150 devices for a school that might have one event in a bad year, things like that. So we need the protections, but we can just do this smarter.

Julie Wang:

So I noticed that Karen has her hand raised.

Karen Murry:

Yes. I don't want to interrupt the flow, but I just wanted to clarify a couple of things that I thought might be helpful. First of all, the discussion about Primatene mist. I do want to clarify, I think this is already alluded to, that it is approved for the temporary relief of mild symptoms of intermittent asthma, not for anaphylaxis. And I also want to emphasize that consistent dose delivery with that device has been a challenge. It's a bit hard to use and the device needs daily cleaning to get consistent delivery.

So I just want to put that clarification out there while acknowledging that there is an inhalable epinephrine out there non-prescription, but for a different condition. And then the other thing I want to clarify, and I think our panelists know that, is that the FDA does not have authority over drug pricing. However, I will say that most of the time when something gets switched to non-prescription, both costs to the consumer and overall healthcare system costs go down for the use of that drug for that therapeutic use. So I'll close there. Again, I didn't want to interrupt, but just want to clarify a couple things.

Marcus Shaker:

I think that's a great point. There is older data that if you use 15 to 20 puffs of the inhaled epinephrine product, you can obtain the same drug levels as you do with injectable epinephrine. They actually rise faster and they fall more quickly. So you're right, people who use that for allergic reaction, it is an off-label indication, but you can actually obtain similar blood level can with products that are approved. The other curious thing is there's probably a lot of drugs that are prescription that have equivalent forms that are non-prescription. A common example is Fluticasone and Azelastine, which is Astepro is available in a higher concentration over the counter than it is by prescription. So that there are some things that we currently have. We're talking about anaphylaxis here, but you could also have a conversation about

asthma with budesonide tramadol, potentially moving to an over-the-counter status. And we modeled that and showed that there would be tremendous health economic benefit. So-

Karen Murry:

Yeah. So thank you for that. I just want to make one clarification also on the inhaled epinephrine for asthma. If it's older data, it may have been with a previous propellant that can no longer be used because it's ozone depleting, and the current propellant that's used in there and the formulation that has to be used is one of the reason that the dose delivery is more difficult now. So I'm not sure that the current device within the current propellant would be the same as the older device that used a different propellant.

Marcus Shaker:

Yeah. I don't know that anybody's advocating that this should be used as an alternative to an approved product for anaphylaxis, but the fact remains that you can buy 20 milligrams of epinephrine right now over the counter for $30. And Neffy is two milligrams from the device [inaudible 04:44:11]. So we have inconsistencies in the way we're currently approaching this. And if you worry about potential side effects from epinephrine, I think you must acknowledge that we're currently in a situation where this drug is available to people in 20 milligrams, it's the fact.

Timothy Dribin:

I think one thing Karen brought up earlier is drug labeling. And I think for some medications, the drug labeling is a lot easier, but I think trying to distill the complexity of a multisystem condition that's dynamic into an easy to use, recognizable thing that we actually think people are going to be able to read and make an informed decision, I think is pretty low. And then also for now saying you no longer need to go to the emergency department, that gets even more complicated. And I think the other reality is that we talk about Narcan, I get too much Narcan in my career, but Narcan is a little easier. When someone's not breathing and they're unconscious, that's it. That is pretty rare with anaphylaxis.

They're usually pretty anxious talking to us, all that stuff. So actually think Narcan's a little easier. Same with an AED. An AED is telling you how to apply it. It's telling you, should you give a shock? Should you not give a shock? Imagine if we're trying to have bystander to recognize an EKG rhythm and distill, is this a shockable rhythm or not? No way would that work. So I think the labeling component would have to be addressed to make sure that yes, you have a device, but are we going to give people the information they need to recognize anaphylaxis and then to be able to be reminded when they need to pick up another epinephrine device when theirs becomes outdated? Those would be some thoughts.

Nissa Shaffi:

Thanks, [inaudible 04:45:56]. So I just wanted to clarify on the insurance piece. So if this were to go over the counter, one thing to consider is the impact it would have on Medicaid patients because Medicaid patients don't pay usually for the most part any copays. And if this were to be made over the counter, they'd now be stuck with the bill of an over-the-counter medicine. This was an argument that was made about two years ago where the FDA was trying to... There was an RFI process for moving birth control over the counter as well, and the big concern was the Medicaid population, their ability to access it.

Julie Wang:

Great. So we have a few questions from the audience and you touched on some already. One person brought up, can you discuss the potential impact of GEO's law that was introduced in Congress, which

would enable law enforcement and other first responders to carry epinephrine? I think you alluded to that, but what are the implications of this in terms of increasing access?

Nissa Shaffi:

So the increasing access to GEO's law, of course, just a brief background of it. It's named after a 14-year-old boy who died from a peanut allergic event anaphylaxis in New York. And the issue there was that his mother was reaching for the epinephrine, realized she didn't have any, then the EMS, law enforcement and fire responders came. They also didn't have it. So improving access to epinephrine in emergency situations is the goal here and ensuring that laypersons and first responders are properly trained and have the resources to administer the drug so that in emergency situations we've heard, especially from your presentation, Julie, about the time sensitivity and responsiveness required for his condition.

Julie Wang:

Great. Another audience question is discuss the impact of insurance coverage on access, including the use of STEPS therapy, even though FDA doesn't have authority over this area. Can you talk about-

Nissa Shaffi:

Sure. Yeah. So with STEP therapy, there's certain legislation that we are advocating for like the Safe STEP Act to make sure that patients have expedited review in terms of accessing these critical treatments. STEP therapy will usually introduces barriers to access to treatment because a patient we've heard throughout the day leaves with one prescription and then has to encounter a hurdle of barriers in accessing that treatment or a suitable alternative. And sometimes that alternative is not something they have training in. It's an unfamiliar product. So suppose they get prescribed with an EpiPen, they end up with an IVQ or end up with a generic when they were supposed to get a branded product. So it's an additional barrier to getting access to the drug itself. So it's-

Julie Wang:

The idea that whatever you get first, you have to fail it.

Nissa Shaffi:

You have to fail to prove that that first treatment was ineffective, so you can move up towards the actual prescription your doctor would prescribe.

Julie Wang:

So that's yet more back and forth between the patient up to [inaudible 04:49:14].

Nissa Shaffi:

Delayed care. Exactly.

Julie Wang:

Okay. Thank you. And then AEDs you already covered in terms of parallels and the differences, but that also touches on the tech aspect that exists within an AED that supports the clinical indication for when to use and when not to use. So do you want to speak a little bit more about that?

Timothy Dribin:

Yeah, I think just from my medical training, I think we've learned that prescriptive recommendations, people like them. Even in healthcare fields where they're trained over and over again about how to manage a life-threatening condition. During stressful situations, that knowledge of what I should do totally falls away. People know what they should do and they panic. And that's why there's a [inaudible 04:50:02] they had the checklist manifesto. That's why airlines checklist reminders of what to do reduces the mental burden on anyone. I think that's even more so on people in community settings that are incredibly stressed out, may have low health literacy, lack of resources. So I think from that situation, we've heard from patients and carers that they want to have prescriptive recommendations.

That they don't want to have to make this decision because there's uncertainty in their stress and that they want to be empowered to have competence. I've heard, I hear if in doubt, give epinephrine. And I get that and I recommend that, but I wish in 2025 we could provide more, give people more confidence to have clarity in their decisions and not just say if in doubt, because we hear over and over again that people are in doubt. There's some people who aren't, but a lot of people are, especially non-primary caregivers like grandparents or homes where it's a single family and there's a babysitter. How do we expect those individuals to make an informed decision when they haven't been trained on this? So I think there's opportunities to provide more just in time resources.

Marcus Shaker:

Quickly on the way to solving that. I mean, you've led a tremendous effort and before long, we'll probably have an app that comes out of that effort that'll help direct people, at least generically in a training sense, and then will be prescribable by clinicians. But even if it's not prescribed, it will have training features. So hopefully the community who is at risk or people who care will have that ability. I mean, I think that you brought up the Narcan example, and that's a parallel that deserves just a bit more highlighting. I mean, you look at the tremendous benefit from community access to Narcan and areas that you really didn't expect it would make a difference and it has. And we know that even if you're not trained on this, there was a study in 2020 that showed that two-thirds of adults who were untrained in a simulated overdose environment with all the chaos could correctly administer Narcan.

And so I think that we sometimes don't give people as much credit as they are due, and that people who are well-intentioned, who may just want to have access and carry around epinephrine for the community may improve that access as well. We did a study years ago where we presented a situation to our patients who carried epinephrine, or their parents. And we presented a situation where somebody was at a local amusement park, Santas Village up the road and they said, "Oh my goodness, my child has just been stung by a bee and they're having a severe allergic reaction." And we asked, "Would you share the epinephrine device that you have?" And not surprising, the overwhelming majority would, but those who wouldn't cited concerns about medical-legal issues or that they may need it for themselves, again, highlighting a lot of what we're talking about here.

Julie Wang:

Thanks for bringing up that study, Mark. Yeah, it's very interesting to see that people are generally altruistic, but there are all these other barriers that come into play.

Matthew Greenhawt:

Yeah. With the when in doubt gave Epi, I think it almost defaults to the other direction when in doubt they don't. And again, it goes back to all the things like it's a deductible, it's an ambulance ride, it's a day in the emergency room, it's a number of things that prevent them, or it's needle phobia or something like that. It is not as easy. The problem is with you and I've had this debate, especially with the paper

and everything like that, a disclosure, several of us are authors on this and collaborators here. I disagree. I don't think it's necessarily our job to tell people to do or don't do. I think we can advise, I think we can consent, but at some level, epinephrine, like it or not, is never going to have a strong recommendation because that's not the way that the evidence is done.

It's not a randomized controlled trial. You don't have millions of patients, it's much like a parachute. You've seen it open. You trust it's going to work. It's experiential type of thing. But when you rate it in a grade format or a guideline format, it is conditional and it's got low certainty of evidence, meaning it's always going to be preference sensitive based on your values and preferences and what you want when you're going to use it. Now, there's no downside to using it. Even with all the cardiac stuff, you're still going to give it because you don't have a better choice and you can always fix the cardiac stuff. You can't necessarily fix the death part if you don't get the epinephrine in that circumstance.

But the fine-tuning of when to use it, we don't have data to say if you don't use epinephrine here, you're going to end up with this outcome. As much as we think we have that, we don't. So it always defaults back to epinephrine sensitive. Again, best alternative, best strategy. We'd certainly recommend using it, but to force somebody into that situation, I still don't think we have the evidence to say that you definitely have to do this or else. And it's different with chemotherapy or some other terrible options. And it's just for whatever it is, it's an unfortunate snag of how epinephrine is researched.

Julie Wang:

Yeah. So I think you bring up a lot of points. Having allergic reaction to getting epinephrine, it's actually not one decision point. It's multiple decisions. And so we don't technically know where on that spectrum that is blocking every individual person. Everybody's a little bit different. I think this app addresses that first point of how do we even know when a bad allergic reaction is happening. Again, just to put it out there, I think within the test world, there's a lot that's being done within other healthcare areas, but it's moving into the allergy space as well, like the wearables to see whether there are vital sign changes or skin permeability changes that are starting that could alert somebody that an allergic reaction might be happening.

And that could, in coupled with an app, let's say, provide more guidance if that first part is the barrier for that patient. So as part of an upcoming trial supported by the Consortium of Radiology Research and each sponsored consortium, there is going to be a safer study that is looking at food challenges. And as part of that, searching for biomarkers associated with positive food challenges, but also looking at a wearable to see whether there are markers that can be seen during the course of symptom development that could support it. And we see this in diabetes. I mean, you can track subtle temperature differences for fertility. So I think that's another big area for tech. So whoever wants to do that research and support that research, I think that's another big area that needs addressed this point number one.

Timothy Dribin:

And I think another thing with considering over-the-counter epinephrine is-

PART 9 OF 10 ENDS [04:57:04]

Timothy Dribin:

Considering over-the-counter epinephrine is, thinking about that, if it's available, then we need to make sure that patients get the right device. If there's different devices that are out there, there may be some

devices that are better for the adolescent college student who's willing to open their mouth, take a sublingual pill, nasal epinephrine.

While a two or three-year-old child, if they're just with their parent, they may not be able to administer some devices. So I think some of the usabilities, some of the more information that hopefully we'll glean once these devices are out there will hopefully make us, I think, make more precision medicine decisions about making sure that it's the right device for the right patient, because I think there's still a lot to learn in that area as well. I would hate for someone to have a device and then not be able to [inaudible 04:57:44].

Marcus Shaker:

Well, and this is [inaudible 04:57:46] either. I mean, we've got pharmacists who can also provide this counseling. And so I think that's a really important piece to remember is that non-prescription doesn't necessarily mean the only option is over the counter. I mean, it could also be a behind the counter sort of thing where somebody reads counseling, but the idea is to remove the barriers to this to open access.

And again, I would underscore what Matt said in that there is no absolute contraindication to using epinephrine. So by creating more access, we're not going to create less ability to treat anaphylaxis. The people who are counseling and seeing patients are still getting that counseling, but now they're going to have more ability to obtain forms of epinephrine that they may not be able to obtain now. And people who haven't seen an allergist will now have the ability to have access to that. So I think that all we're doing is adding to the current situation. We're not really trying to [inaudible 04:58:45].

Nissa Shaffi:

Yeah. Thank you. So I wanted to highlight that in the spirit of forward-looking strategies. This is the time to start cultivating those relationships with health plans so that they can offer those point solutions with the wearables, with those monitoring devices, because there often a lot of health plans are even funding the CGM research in partnership with these institutions. So if there is a product on the horizon for anaphylaxis, I think the conversation should go in that direction. I'm sure it is, but just offering that.

Julie Wang:

Yeah. That's a great point that it's not just one stakeholder that's involved in any of this. It's multiple stakeholders along the entire very long journey to get something in the hand of patients [inaudible 04:59:31].

Matthew Greenhawt:

Yeah. I mean, going back to the OTC thing, I just want to make sure that we want responsible use. And I think I could go into the drugstore now and pick the wrong dose of something over the counter, and that happens. I think we need to make sure that we're not forwarding very unlikely arguments or whatnot. Switching from the allergist expert role to the advocate in the advocacy world, we need to trust our patients.

We have a problem. People who need it don't use it now. People are not all of a sudden just going to go buy it and you now all of a sudden surreptitiously use it. That's probably not the most likely outcome. So we have to trust patients that they're not ... If you've never had epinephrine, it's not the most enjoyable ride. I mean, I guess it is for somebody out there, but that's not how you want to spend your Saturday morning or something if you can help it.

Especially if you're getting a needle or something like that or whatever the sensation is. But trust the patients that we need to help them get something that they want to choose. The Epi that you choose and carry with you is the one that you're far more likely to use, hopefully. Not a perfect sort of transition there, but we need to not be paternalistic and be too prescriptive of practices for patients. We've done that. We've made mistakes in the last 10 years.

Some of us in the room have been on guidelines where we clearly blew it. We wrote something, we thought that this is going to be a great idea and it blew up in our face. So we need to trust the patients. We need to give them a choice and realize that if we do our job and counsel them in the right way, that they will make the right choice. And we don't have to do anything, but just put the information out in front of them.

Julie Wang:

So I'm going to go to an audience question that kind of tangentially relates to that. So if epinephrine were available over the counter, would speakers recommend that patients still see their allergists and other PCPs regularly, even if they don't have to see them in order to get an FPV fill? Yeah, of course. [inaudible 05:01:33] but yeah.

Matthew Greenhawt:

I can muck around under the hood of my car, but I'm going to go to a professional. That's not going to end well if I'm trying to do this all myself. I mean, for some people, if you're underinsured or you're uninsured, it does give you some safeguard if you can afford it. This is going to balance out, the people that we think are just going to hoard it and overuse it versus the people who can't get it by any other means now can get it. I think still you want to get the right diagnosis. It's just a little bit of an extra safety net. And you look at risk/benefit of using the medicine, there are very few, almost implausibly no instances where you'd really say, "You know what? You shouldn't use that under any circumstance and you can't tolerate it for five, 10 minute excursions or whatnot."

Julie Wang:

Right. Yeah. So I completely agree. I think our value as physicians are way more than as prescription writers. We're going to ensure accurate diagnosis. We're going to monitor them over time because kids can naturally outgrow their allergies. Dr. Sampson already mentioned that there are treatments that are currently approved and are available to patients and their families. Going to a local pharmacist to pick up their epi doesn't negate any of that necessary discussion that must happen and that we provide as physicians. Marc, any other physician [inaudible 05:02:55]?

Marcus Shaker:

[inaudible 05:02:57]. It's kind of a carrot and a stick argument. I mean, there shouldn't be a barrier to epinephrine such that somebody has to go and see me to basically do what a pharmacist would do, and they should have access when they need it, when they feel that they need it. Just like you all said, the tremendous added value of allergy immunology in 2025 is, it would've been hard to predict 10 years ago what we're able to with biologics and with glutamine therapy and desensitization, counseling and shared decision-making.

And perhaps that's really where the value is. It's being able to talk with somebody who's seen a lot of patients like this and who's up on the current literature and can be a guide. I mean, I like to say to my patients, "You're the navigator of the ship. You're the captain of the ship. I'm the navigator. So I will help you go where you want this ship to go." But this whole conversation is about really helping empower

patients to have the tools that they really do need, and then they can still come to us as a partner and a guide, but not as a vice principal so to speak.

Julie Wang:

Yeah. And I'll also add that obviously we're speaking from the allergy perspective because we're trained specialists, but primary care providers also are super important for these patients to go to because they're the doctors that these families probably see much more on a regular basis and have a very established relationship and can help families navigate daily life situations, school transitions, school forms for that matter, camp forms. So again, speaking to this question that came in, having epinephrine over the counter is not going to negate the need for someone to show up at a physician's office. Go ahead.

Matthew Greenhawt:

I was going to say, we haven't seen that with inhaled nasal steroids and antihistamines, and that was a big fear. I mean, my gosh, I remember all the time I wasted doing prior auths on that stuff. I mean, thank you FDA for making my life much easier at the tail end of my fellowship, but I don't think it has deterred our ability to diagnose allergic rhinitis or whatnot. And I think there's always some nervousness about how that's going to play, but I think we need to trust the patients that they're going to do the right thing and they're not going to cut us out of this deal. It'd be very hard for us to be cut out, I think.

Marcus Shaker:

And I wrote a prescription for cetirizine today, so doesn't mean prescriptions won't still happen.

Nissa Shaffi:

We also need this data to drive policies. So even if it's available over the counter, patients still need to have a relationship with their physician so that they can be informed and that we could have the information as policy advocates to drive the decisions that need to be moved forward.

Julie Wang:

And then another, so audience, please keep the questions coming through Slido or Zoom chat. But another question came in about what do you think the effects of online information, environment and potential misinformation on appropriate self-treatment [inaudible 05:06:10] patient of Dr. Google, et cetera?

Matthew Greenhawt:

I mean, I've never read anything that's wrong on mine. The great thing is I can find what I'm looking for. [inaudible 05:06:20]. I mean, as I watch my son slowly become sort of radicalized and grow science online with other things with his weightlifting and his protein, I mean, it is amazing the messages that get pumped out to somebody who wants to learn and is eager. I mean, there's a balance with everything, but it's not isolated to healthcare. I would say healthcare is probably not the main concern with misinformation online right now, but that's just my opinion.

Julie Wang:

Yeah. And I think any changes that gets made about how epinephrine is prescribed is not going to happen in isolation. It's not like we're all in this room will just keep our mouths shut. Our job is to

continue to educate and disseminate true, accurate, evidence-based information. So again, while online misinformation may be possible and may affect people picking up epinephrine by themselves, that doesn't change our job regardless. Okay.

Marcus Shaker:

Yeah, I would echo what [inaudible 05:07:21] said in that the misinformation we have in our society is not around epinephrine per se. And you actually do see a nugget of a potential future with open evidence, these kind of platforms that are AI driven, but are very well referenced and very well vetted. And so you wonder if the future is going to, through AI, through reliable AI, through AI that is vetted and well-cited with real papers, not for 10 papers, whether or not we'll reach a point where this becomes more open and we begin to have a more common understanding of what the truth is, these sort of things. But we're not quite there, but you wonder if that's where the future might take us.

Julie Wang:

So thinking that part of technology would have to be a positive advance where the truth tips the balance somehow.

Timothy Dribin:

Yeah, it's funny you can go into Copilot or whatever it is, ChatGPT and say, "Should I give epinephrine," and list the symptoms, and it gives you a response. And sometimes it's pretty darn good if it's referencing the right thing. So I think what Marcus said, if it's referencing evidence-based articles and everything like that, there could potentially be a role.

Julie Wang:

All right. So I think we've already started veering in this direction, but what further research needs do you think should be addressed in the area of anaphylaxis and epinephrine? What are the questions that we should be thinking about, designing studies to look at? [inaudible 05:08:51].

Nissa Shaffi:

I think the study should be ... well, we need data basically from a policy perspective. So I'm going to go back to stocking laws again. If there are states that permit stocking versus states that require what is that economic impact, how do we advocate for the right decisions to be made? Who needs to be part of those conversations? And when more delivery systems come out into the market, how do we move those conversations forward in that respect as well?

Matthew Greenhawt:

I'm fascinated by all. So much has been learned by just watching the development of new epinephrine products, but also looking at the performance of things that we assume worked in such a fixed and predictable mechanism, just seeing it blown up, that three companies doing the exact same experiment with the same device in three different thighs gets variably different answers, but yet all of these work. So how do we optimize route and form and dosage?

And if you look at some of the data coming out of Imperial, looking at what parameter in resuscitation and distributive shock is the most important, do you want MAP? Do you want your stroke volume? What is key? How fast does it have to act? What is our buffer? All of these work, so it gives patients a choice. And we want patients to have a choice so then they'll pick something. What we have now is

probably not the ideal because it's basically one form, a variation in the same form. Give them different routes, so they'll at least use it. But understanding are the outcomes different? How do you optimize things with that? So again, I think that that's the next step.

Timothy Dribin:

I think Chris brought this up, and Ruchi, that the quality of our data is pretty poor, especially from a population health setting. A lot of our data is from EMR and emergency department's databases and oral food challenge clinics. So I think a higher quality prospective study, a registry to really figure out what's the prevalence that's out there across the different ages, what's the rate of ED utilizations triggers? I think that'd be helpful.

And then there's really never been a, that I know of, a large head-to-head clinical trial on anaphylaxis. So I think some of the big questions are, we brought it up, but does giving epi to someone who does not yet have anaphylaxis, do those patients do better? We think maybe it does, but we don't really know. So I think there's a lot of thoughts that people have that are not really backed up with great data. And I think doing a clinical trial, especially I think like an oral food challenge clinic, I think it would be feasible to do that stuff. So hopefully in the future that could be accomplished, I think resolve some of the gaps in there.

Julie Wang:

Mark?

Marcus Shaker:

I mean, I think there's a lot of interesting work to be done on our non-injectable routes of epinephrine actually superior to injectable routes, because if it's inhaled and it's getting into the airway and you're having bronchodilation at the same time, you're delivering epinephrine. If you're taking it sublingually or by nasal route, are you not hitting the beta receptors that are causing a reflexive decrease in some of the diastolic blood pressures? So I think that there's a lot we think we know about epinephrine. There's a lot that may be a little different than we think we know. I mean, the role of mast cell stabilization. So I think that that would be very interesting to have more comparative evidence on epinephrine during actual allergic reactions.

Julie Wang:

I think with the newer devices, that's really opened up a world of questions that we didn't really question so much before, because we just accepted that this is what you do. An area that I think does need looking into is about the barriers. I think we've made a lot of assumptions that, "Oh, it must be the needle and that's why they don't want to use it." And so once the non-needle comes out, then boom, everybody's going to be fine because they're going to be using their Epi right and left, but that's not the case.

And I think it really opened up my eyes when we started offering, "Here are your choices for epinephrine." And one of my patients said, "Oh no, I'm happy with the injectable." And we said, "Oh, you are. Okay. Then you didn't really want to use it in the past." I'm like, "Oh, afraid of needles. That is not a problem." And I think that question didn't really come up because I think we just all assume that that must be the issue. And so I think there is a lot more nuance in there in terms of what's making people hesitate. And so that is an area of research that can delve much further because we can't use old data to support why one device might be better or not better.

Matthew Greenhawt:

I mean, three years ago, I never thought of asking somebody needle phobic or not because it didn't matter. You didn't have a choice. And I almost didn't want to know. I would deal with the outcome if they didn't use their epinephrine or something like that. But now you can have that discussion and you really can tailor it to their preference. And again, there are still limited options. So you've got one additional form, but it's a great option for somebody if they want it. And if they want, there are five or six different injectable forms. Each you're going to get, we're going to move into a direction with more innovation.

Somebody should be able to take something to the ... I mean, again, it's like your worst nightmare of using it, but at least you can tailor your worst nightmare to make it as comfortable for you as possible. If you really want to open up a can of worms and the original red pill, blue pill question is, what if they had actually done studies giving subcutaneous into the thigh, because they never did that. And you look at some of those old levels and they're pretty interesting. And so I mean, again, we know less than I think we did before, but we know that these all work, so that's the most important thing.

Timothy Dribin:

I think one other area still is that the whole, you can do the watch and wait and stay at home, I like this approach. I think some families are hesitant to give that because they don't want to go, ED costs, but there are patients that need to go to the ED, those 2.5%, 1% that will die if they don't go. And I think I worry that we get overly simplistic and say, "Oh, 90% respond to one dose." It's very hard to predict who those non-responders are.

And we better make sure. My big worry is that we try to say, "Oh, you're fine, you're fine." And there is that young child, that infant at daycare who are at the babysitter's watching. That kid's not fine and they need to go. And some families want to go. If you come into the ED and it makes you more comfortable, I want to be able to make you more comfortable. And I think families should be empowered to do what's right for them because not everyone's the same and they all have different circumstances that influence their decision making.

Julie Wang:

And then [inaudible 05:15:47] your research.

Marcus Shaker:

Kind of on that, Tim, I think you're right. I think that if somebody takes epinephrine and they're asymptomatic, asymptomatic people don't really need ERs. But the question is, how do we predict who's going to be at risk for the biphasic? And as a corollary, how long do those patients need to be monitored? And that's something that we're kind of trying to work on. The other thing that I would add is we end up talking as allergists about the diseases people have. We end up talking as doctors about this [inaudible 05:16:18].

But I think it's also important to think about health expectation and help people realize that everybody has more wellness than disease. And how do they begin to appreciate when epinephrine does work and realize that they're empowered to treat these reactions and realize that they're not vulnerable, that they're not an allergy walking around. There's somebody who has an allergy and they take risks in life just like people who don't have alcohol. I think that's the other aspect we need to build into that too and help people appreciate the component of wellness within chronic health conditions.

Julie Wang:

And then I'll add one other category that we haven't touched on, but there is a lot of research in this area is really looking at phenotyping people with food allergy and other allergic issues to try to identify ... We've identified certain risk factors like the elevated basal tryptase. There are certain categories of patients that are at higher risk for having more severe symptoms. And so there is a lot of research now delving further into not every food allergic person is the same, not everybody with hives is the same.

So delving more into phenotyping people, their thresholds may be different. Who are the individuals who have low threshold, meaning they react to trace exposure versus someone who takes a peanut or more to react. Not that necessarily that higher threshold people are completely immune from severe allergic reactions, but maybe their chances of bumping into two peanuts is lower than someone's chance of bumping into a fraction of a peanut.

So that's another whole area of research that is very active so that we can maybe make life easier, a bit easier for patients to say, "You know what? You have this allergy and you do too, but you're at somewhat higher risk and you're going to more likely need to use your epinephrine." And then on the other realm is the treatments that are in food allergy seeking to increase the threshold of allergy. There are also other medications looking at the anaphylaxis cascade and blocking other molecules within that cascade for maybe shorter term protection. So that's another area that deserves a lot of research.

Matthew Greenhawt:

Yeah. I mean, there's a difference between, is it a single spin of roulette where the ball has no wheel, or are you playing a single deck game of cards where if you remove a card or two, it changes and are events linked versus independent. And I think the most important thing is it's not that, I think we do have enough data out there. I think we narrow our approach that we try to pre-specify what we think phenotypes are as opposed to using unspecified data methods, latent class analysis, other things, cluster, [inaudible 05:19:05], things that can tell us what do these patterns look like.

As opposed to us saying, we wanted to fit these bins, let the data tell us what the bins are, then we can name them. And that's the type of approach that we need as you can get into more sort of genotype, phenotype interactions and things like that, maybe we can tailor it, but still there's ... I don't know if we're going to get ... [inaudible 05:19:26] get there in our career lifetime, but ...

Julie Wang:

Which to be optimistic [inaudible 05:19:30].

Matthew Greenhawt:

Canada's going to win a cup in the next 20 years.

Julie Wang:

Great. We have just a few minutes left before we wrap up. So I'm going to give each of our panelists one minute last [inaudible 05:19:48] your thought. Marc, you go first.

Marcus Shaker:

This is just such an exciting venue and such an important conversation that we're having, and it's great to hear your perspectives and the perspectives of everybody who's gathered here. So again, gratitude and wishing everybody happy holidays and save travels home.

Timothy Dribin:

Yeah, no, this has been very optimistic and I think it just shows that there has to be a team science collaborative approach to addressing these very, very complicated problems that span from basic science to implementation science, health economics, and then making sure that we're listening to our patients and caregivers and not trying to make it overly simplistic, because there are a diverse group of people who want different things. So thank you for inviting me, and this has been a really productive meeting.

Matthew Greenhawt:

I echo what he said. I'll double down that we should not assume what a patient wants, and we're only going to learn if we ask them and think about all the outcomes, food allergy trials, anaphylaxis, whatnot, investigators can make an assumption of what we think. But I mean, there are three organizations, four organizations, five organizations represented here, probably more. I'm miscounting but marginalizing and I apologize. But think of all the patient organizations out there, we have members who are dying to give their opinion on something and we're there to help capture that and pair it before we do studies, before we sink money into things that can help.

Nissa Shaffi:

Yeah. Thank you, Julie, for moderating a great discussion and for the opportunity to be here today. We just want to reiterate our commitment to ensuring that patients have access to the drugs they need, and that they're able to do so at a price point that doesn't break the bank, especially in these economic times. And we're just committed to making sure that they have the education and resources that will make that possible. So thank you again.

Julie Wang:

Yeah. And then I guess this is my takeaway from today is clearly there are just so many facets to this issue, this question, that it's not just the healthcare provider, it's not just the legislator, it's everybody's stakeholder in this. Patients and families have very important perspectives. Our patient organizations help bring that to the forefront. And so as we do research and develop policies, we need to hear what the patients and families need. So with that, I will thank everyone for this excellent discussion and close out this meeting. I'm going to turn it over to Dr. Karen Murry, acting director of FDA's Office of Non-Prescription Drugs to close out the meaning for us. Dr. Murry.

Karen Murry:

Okay. So I'd like to express our gratitude to all the participants and all who submitted comments. FDA really appreciates your input. FDA depends on hearing from stakeholders to inform our decision-making. We will review all the comments, including those that were not addressed in the sessions today, and we will examine all the input in toto and determine next steps. As I've emphasized, we'll consider all potential ways to increase epinephrine access, not just non-prescription. We are excited to try to move forward ideally on multiple fronts. And now I'll turn things back over to Brian Canter for his final remarks.

Brian Canter:

Thank you, Karen. I'll be brief. I know people have planes and trains and automobiles to catch. I want to thank Dr. Murry and everybody, all the speakers, everyone who traveled here to DC and everyone who tuned in online. It took a real group effort. It was a team project to get this meeting accomplished. And I thank our colleagues on the FDA side, Nushin Todd, Martha Lenhart, Dorothy Chang, [inaudible

05:23:44], Kelly Stone, Linda Jong, Jennifer Land helping today, Quinn Winn, and the great Fong Bam, keeping them all tied together. And then lastly to our team at Duke-Margolis, Mattie Cordle, Thomas Roades, Val Parker, Matt Dimbrogio, Mia Williams, Hanna Vitiello, Luke Durocher, and Garrett Hamre. We really appreciate everyone tuning into this workshop and have a wonderful holiday season. Thank you.

PART 10 OF 10 ENDS [05:24:11]