UNITED STATES FOOD AND DRUG ADMINISTRATION

FDA PUBLIC WORKSHOP:

APPROVAL OF NEW PATCH TESTS FOR THE DIAGNOSIS OF ALLERGIC CONTACT DERMATITIS

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A G E N D A

Epidemiology and Impact of Allergic Contact Dermatitis

Welcome & Moderator:

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Regulation of ACD Diagnostics

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Designing ACD Patch Tests for Maximum Sensitivity and Specificity

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P R O C E E D I N G S

(8:30 a.m.)

DR. KASLOW: Good morning and welcome to today's FDA Public Workshop on the Approval of New Patch Tests for the Diagnosis of Allergic Contact Dermatitis, or ACD. I'm David Kaslow. I'm director of the Office of Vaccines Research and Review here at CBER, and I'm pleased to open today's discussion on this important regulatory topic on behalf of the team here at CBER who actually overcame a number of challenges to make this workshop happen during an ongoing lapse in appropriations.

So I suspect all in attendance are aware that allergic contact dermatitis affects approximately 15 percent of the population and represents a significant burden on our healthcare system. I also suspect all of you know that accurate diagnosis is essential for effective patient management, as avoidance of identified haptens remains the cornerstone of treatment. I also suspect all of you know that there are over

4,000 substances that can cause ACD and that the American Contact Dermatitis Society core allergen series identifies 100 prevalent core allergens recommended for comprehensive testing.

Today we have licensed patch tests that cover a little more than a third of those core allergens. So we are here to discuss the significant diagnostic gap in licensed patch tests for the remaining core -- prevalent core haptens.

As you'll hear, despite most patch tests delivering small molecule entities, patch test allergens are currently regulated as biologic products under Section 351 of the Public Health Service Act. And since a 1986 Federal Register Notice, any chemical or reagent intended for commercial marketing and used for patch testing in humans requires licensure as a biologic product. To be licensed as a biologic product, patch tests must meet the regulatory standard showing that the products are safe, pure, and potent, with potency generally considered to be demonstration of substantial evidence of effectiveness and

substantial evidence of effectiveness generally established through adequate and well-controlled clinical investigations.

With this current landscape in mind, it seems we face at least four key interconnected topics that this workshop aims to discuss.

First, the current clinical trial paradigm. We acknowledge that the traditional phase and 3 clinical trials, while appropriate for many biologics, presents challenges for patch test allergens. Many individual allergens affect a relatively small patient population, making large-scale recruitment challenging, and we also recognize that the number of studies and regulatory submissions required to individually evaluate each one of those core prevalent haptens is daunting to consider.

Second, the absence of gold standards. Unlike many diagnostics tests, patch testing lacks a definitive standard of truth or surrogate comparator. Clearly, this impedes traditional sensitivity and specificity determinations and

leads to considering less optimal alternative endpoints, such as positivity ratios and reaction indices.

Third, the unique benefit risk profile. Patch test haptens are applied topically to small skin areas, typically once in a patient's lifetime with minimal systemic absorption. The safety profile of patch tests differ markedly from most other biologics, which needs to be considered in clinical safety evaluation and safety database expectations.

Fourth, the economic realities. We recognize challenges faced with navigating costs associated with adequate, well-controlled clinical investigations, with current PDUFA fee structures and other barriers for patch tests that may have limited market potential.

So the goal of today's workshop is to discuss these interconnected topics and explore paths forward that maintain scientific rigor while addressing practical challenge. The three sessions in today's workshop are designed to,

first, review the current evidence based through presentations on epidemiology, occupational contact dermatitis, economic burden, pediatric considerations, and the experience of the patient. And the goal of this session is to establish the clinical and public health imperative of for expanded patch test availability.

Second is to examine the regulatory approaches both here in the U.S. and internationally with presentations from CBER and our Canadian and European colleagues. And the goal in this session is to paint as clear a picture as possible of how regulatory agencies are addressing the current challenges of expanded patch test availability, including the use of real-world data and evidence.

And third, to discuss practical implementation through an industry perspective and review of current testing practices, gaps, and alternative diagnostic approaches. And the goal in this session is a candid discussion of the current realities on the ground faced in

addressing the significant diagnostic gap in license patch test for the remaining prevalent core haptens and ideate on ways forward.

A key desired outcome to today's discussion is to hear from you. We need your expertise to help us understand where current regulations may be burdensome and where flexibility can be introduced without compromising safety or effectiveness. We're interested in hearing how to adapt traditional clinical trial requirements to the unique characteristics of new patch tests for the diagnosis of the ACD, while maintaining the scientific rigor that ensures accurate diagnosis and meets regulatory statutes and standards.

The path forward, undoubtedly, will require collaboration among all stakeholders, clinicians, researchers, industry, patients, and regulators. So as part of that collaboration and path forward, your participation today is an important opportunity to take a critical step toward ensuring that healthcare providers and

their patients with allergic contact dermatitis have access to comprehensive tools they need.

Before we begin our sessions, just a few housekeeping items to ensure our virtual day to today runs smoothly. Please use the chat box for questions throughout the presentation. We'll address as many questions as time permits during each session and our panelists will be available for discussion periods. Please send any additional questions that occur to you after today's event to CBERPublicEvents@fda.hhs.gov with the subject line ACD Workshop. Please note that the workshop is being recorded and will be web hosted.

Finally, I want to acknowledge the tremendous effort that has gone into organizing today's workshop. From CBER, I want to thank Sharon Tennant and Ron Rabin from our Office of Vaccines Research and Review, as well as Loni Warren Henderson and Stacey Rivette from our Office of Communications, Outreach and Development. And we are also grateful for our

academic partners, Jeff Yu at the Virginia Commonwealth University and Dr. Alexandra Flamm from New York University. Their expertise and collaboration have been essential in today's agenda.

So as we embark on today's discussion, I want to emphasize that our mission here in OVRR remains unchanged, and that is to protect and enhance public health and public trust through both regulation and research. Assuring available regulated products such as patch tests are and remain safe, pure, and potent for their intended uses. We recognize that inflexibility may not always serve patients best. And today represents an opportunity for all of us, regulators, industry, academia, clinicians, and patients, to work together toward new ideas and solutions that serve patients while maintaining the safety and effectiveness standards they expect and deserve. I am personally excited about the discourse ahead today and look forward to the insights you'll share. So thank you again for joining FDA today.

And without further ado, let's get to work. So first up on the agenda is a presentation on "Epidemiology and Pathophysiology of Allergic Contact Dermatitis." That will be presented by Dr. Alison Ehrlich, who is a board-certified dermatologist and is the former founding chair and director of clinical research and in the Department of Dermatology at Georgetown University, who is now in private practice in Chevy Chase, Maryland.

Alison, to you.

DR. EHRLICH: Yeah, can you hear me now?

DR. KASLOW: Great. Yes, we can.

DR. EHRLICH: Okay. Good morning, everybody. Sorry for the audiovisual issues. Apologize on that end. Today I'll be talking about history, epidemiology, and pathophysiology of patch testing. Next slide. Are you all advancing for me?

DR. KASLOW: Yes, we are.

DR. EHRLICH: Okay, next slide. So there is some animation in here, but we'll get to

that.

Okay. So this is an overview of what I'm going to talk about today. I think you just jumped ahead. Can you just get back? Thank you. I'll just tell you one to advance, please.

Okay. So I'm going to be going over what are allergens. So I think it's really important for everybody to understand that we're talking about topical allergens. We're not injecting allergens into the skin. These are all topical. We'll be talking about what is patch testing, the difference between allergic and irritant reactions. So we, when we are patch testing, are testing for allergic reactions. We are not trying to figure out what is causing an irritant reaction. It's the allergic reaction we're going for.

I'm going to talk about the history of patch testing. I feel that this is very important because patch testing has a long history of use and this tells us a little bit about the safety track record for patch testing. I'm also going to

talk a bit about the epidemiology of patch testing. Next slide. Next slide.

Thank you. So what are we doing with patch testing? We are testing for delayed type 4 cell-mediated hypersensitivity, so we are applying topical allergens. This is very different than prick or scratch testing. So prick or scratch testing, in that case, you're testing for immediate type IgE hypersensitivity. So we're talking about two very different pathophysiologies, different types of testing. So it's important to know the difference. Next slide.

So while we're -- thank you. So, topical allergens, these are low molecular weight, less than 500 daltons. They're lipophilic. So what's important about that? So being small and lipophilic, they can cross the epidermal barrier and they're able to interact with the immune system of susceptible individuals. So this is what we use for acquired immune-related inflammatory reaction testing for type 4 testing.

So some of the things we're going to be testing for would be things like hair dyes, fragrances, preservatives. That's very different than what we would be tested for with intradermal testing. Intradermal testing, you're working up patients to see if they have allergies to things such as dust mites, ragweed, different foods. Next slide.

So there are two phases with the development of allergic contact dermatitis. So we think of the sensitization phase and then the elicitation phase. So this helps to explain why with delayed type hypersensitivity reactions, you don't necessarily develop a reaction with the first exposure. During the sensitization phase, epidermal antigen presenting cells, such as Langerhans cells and dermal dendritic cells, present low molecular weight haptens to T cells in a draining lymph node in association with major histocompatibility complex class 1 and 2 where they prime naive T cells. Then T cells differentiate into effector or memory cells.

And, pardon me, the activated T cells

then travel between the lymph nodes and the skin. Sensitization can take 10 to 15 days.

During the elicitation phase. Now, an example of this is this patient that was a butcher developed an allergy to rubber accelerators in his rubber gloves and was chronically developing worse and worse dermatitis while at work, so he had significant occupational dermatitis. So during the elicitation phase there's a re-exposure to the same hapten, in this case with the butcher the rubber accelerator. And this induces antigen presenting cells to present the hapten protein complexes to memory and effector T cells.

Additionally, keratinocytes and Langerhans cells secrete pro-inflammatory cytokines, such as IL1B, TNF-alpha, along with chemo attractants as part of the innate response. As a result, T cells travel to the skin and there's an increase in the proliferation of antigen in specific T cells leading to this cutaneous inflammatory reaction and upregulation of the immune system, which results in dermatitis

that we see clinically. Next slide.

So there's some animation here, so you can click so it all comes on. I think that's going to be easier in this situation. So patch testing, what do we use it for? By reproducing the elicitation phase for specific allergens, we're trying to discover what are the culprits that are causing dermatitis in a specific patient. Can you click on the animation so the rest of the slide pops up?

Thank you. So we're looking to improve -- so we're looking for causative agents of presumed allergic contact dermatitis in patients who have recurrent dermatitis. We're also looking to help patients who have chronic dermatitis, such as preexisting chronic dermatitis, such as atopic dermatitis, who are now presenting with increased flares in specific areas or worsening dermatitis. And we're looking to figure out why is it worsening even though we're treating it?

We're also hunting for causes of occupational dermatitis and also drug-induced

dermatitis. So there are definitely situations where patients have been on several different drugs, they're developing a skin eruption and they need to be on a specific drug. And it's really important to figure out what is causing that skin reaction.

So there are several different situations in which patch testing is incredibly useful in the clinical setting. And I think one really important take-home point on the utility of patch testing is definitive diagnosis through patch testing has a really critical and positive impact on the quality of life of our patients with dermatitis and also can be very cost-effective in working up patients for recurrent dermatitis. Next slide.

So it's important to understand that with patch testing, again, we're really trying to test for allergic contact dermatitis, not irritant contact dermatitis. So what is the difference? So with allergic contact dermatitis, there are cutaneous sensitizers such as topical allergens,

and they cause delayed skin reactions, not necessarily after -- always after that first exposure. They also can cause reactions not only in the area where the skin was exposed. You can get generalized reactions. You can also get airborne allergic contact reactions. With irritant contact dermatitis, this is very dependent upon the direct interaction with the skin at the site of contact. And can you click again? There is an additional little point that needs to go on this slide, please.

This is dependent on the intensity and also the time duration of reaction. So example, again, going back, patient with like Rhus dermatitis, poison ivy dermatitis, so that they're directly in contact with that plant and developing dermatitis. We're not patch testing for Rhus dermatitis, but that is an example of allergic contact dermatitis. Example, hand irritant contact dermatitis, bartenders, housekeepers, chronically getting their hands wet for many hours at a time and potentially working with irritating

chemicals, so that chronic exposure with wet work breaks down the skin barrier and they frequently will develop dermatitis. Next slide.

So the history of patch testing is really quite fascinating. Patch testing has been around for many years. So in 1895, Josef Jadassohn presented a paper on the functional skin test, which was the original patch test, at the 5th Congress of the German Society of Dermatology in 1895 in Graz, Austria. So this was considered the birth of patch testing. Marion Sulzberger went to Europe and worked with Jadassohn and then came back to the United States. He published the first major publication in the States, "Allergic Contact Dermatitis: The Contact or Patch Test and Dermatitis and Dermatology," with Fred Weiss.

In 1937, Bruno Bloch presented work on standardized gradation of reactions and allergens. And one of his students, Paul Bonnevie, in the 1930s expanded upon Bloch's work and proposed standardized series of testing substances to establish the etiology of contact dermatitis. In

the early '40s, Chase and Landsteiner presented work on contact allergy and delayed type hypersensitivity using guinea pig models showing naive lymphocytes could be transferred. In 1962, the Scandinavian Committee for Standardization of Routine Patch Testing was created. This led to, in 1966, the International Contact Dermatitis Research Group was formed and this was significant towards standardization of patch testing. Next slide.

In the United States, while we know that Sulzberger started clinics at NYU, the North American Contact Dermatitis Group became a committee under a subset of the American Academy of Dermatology, the DSI, in the 1980s. In 1988, Bob Adams ran the first symposium on contact dermatitis. Later that year, there was an AAD committee that was formed by members of the NACDG and guided by Robert Rigel. And then in 1989, the first meeting of the American Contact Dermatitis Society was held. Next slide. Next slide.

So we're changing gears a little bit and

talking about what is tested with. So the TRUE, thin-layer rapid use epicutaneous, Test was first approved 1994 in the U.S., and this had 24 allergens and 1 negative control. It was expanded in 2017 for children and additional allergens, 35 allergens and 1 control, and designated as an aid for the diagnosis of allergic contact dermatitis. Next slide.

Can you just keep on clicking so the whole slide appears, please? Thank you. So additional testing that is done includes the North American Contact Dermatitis Group series and the ACDS core series. 1972, first NACDG tray was introduced with 19 allergens. That was expanded in 1981 to 20 allergens. The current standard tray has 80 allergens. And the ACDS has published on a core series that would allow dermatologists to do a broad testing for patients. That was first introduced in 2009 with 80 allergens and expanded in 2020 to 90 allergens. Next slide. Next slide. Next slide.

DR. KASLOW: I'm on the next slide.

DR. EHRLICH: Okay, thank you. In 1970, the ICDRG published on a grading system for patch test reactions. This included several different categories of reaction, starting from doubtful to a very strong reaction. Two other categories, irritant reaction and not tested, were discussed. Next slide.

This was actually expanded in 2024, which I'll go over. Okay, great. Thank you. Can you please click? There are several things that become highlighted.

So the key things to recognize on the expansion. For more detail -- can you please keep on clicking? There are some red circles that come up. More detail on downfall and weak reactions to reduce confusion between these two categories. And then a new category was added which dealt with presently unclassifiable reactions. These are reactions that spread beyond one category. Next slide. The original -- next slide.

The original relevance was published early in 2001, looking at definite, probable,

possible, unknown, or past. So relevance is actually very important for helping to counsel patients on the importance of which allergens are going to be key and critical for resolving their dermatitis. Next slide.

So as far as epidemiology of skin disease, this is looking at AD burden of skin disease publications, 85 million Americans, 25 percent of the population, 1 in 4 individuals were seen by a physician within a year for skin disease. Contact dermatitis affects 15 to 20 percent of the general population over lifetime with 5 to 10 percent having symptoms every year. So contact dermatitis is a significant part of skin disease for Americans and even -- and worldwide. The average cost per patient is approximately 887-- $900 a year. Direct costs can be 75 billion and indirect costs are also very high for skin disease. Next slide.

So you see that contact dermatitis affects many people. It is very costly and thus patch testing is a very cost-effective mechanism

for determining what is causing skin allergy, contact dermatitis. And I think it's worth noting that from the North American group that if you look at several different time periods, there's great consistency between the data in that when you patch test patients, approximately 70 percent tested will have at least one positive allergen and approximately 50 percent of those will receive a primary diagnosis of allergic contact dermatitis. So thus, we see that patch testing is a very useful and cost-effective tool for dermatologists and allergists. Next slide.

So this is data from a meta analysis of 28 studies from 2007 to '17. So this is showing at least 20 percent of the general population have contact allergy to common allergens. The prevalence is higher in women. Nickel and fragrance are two of the big allergic groups that we see, and this is in adults. Next slide.

When you go on to look at the data on children, what we see is that metals and fragrances also come up pretty high. We also see

some surfactants, such as cocamidopropyl betaine, topical antibiotics, and, interestingly, methylisothiazolinone is higher in the U.S. than Europe because Europe does regulate contact allergens a bit more in products. Next slide. Can you please -- yeah, great. Thank you.

So when looking at the burden of disease and different skin diagnoses, what we see is that contact allergy is one of the higher prevalence categories within different dermatology diagnoses. So it is very important and something that we frequently see in our clinics. Next slide.

So looking at occupational allergic contact dermatitis, briefly, what we see is the prevalence is actually very high, 6 to approximately 10, 11 percent. Eighty percent of cases of occupational contact dermatitis involve the hands. So this causes significant morbidity and cost in the workplace. And there are several categories of high incidence occupations, which would include agricultural workers, construction workers, healthcare workers, hairdressers,

mechanics, and machinists. And this is really important. In 2020, occupational hand dermatitis had an incidence of 1.8 per 10,000 workers, making it the second most common occupational health concern being tracked. So these are really important to determine what is causing this dermatitis. And also patch testing is very cost-effective in working these types of reactions up. Next slide.

So, in summary, allergic contact dermatitis is a common diagnosis in the general population where seeking dermatological evaluation. Comprehensive patch testing is a vital method for the evaluation of allergic contact dermatitis. And we are using topically applied allergens that are considered very safe, and patch testing has been around for a very long time. The preservation of this tool and the haptens for testing are critical.

And thank you. I appreciate your time.

DR. KASLOW: Thank you so much for that review of the epidemiology pathology of ACD and

the history of patch testing, and really making the case that definitive patch testing is a cost-effective tool in the diagnosis and subsequent treatment.

So we're going to have about a 45-minute Q&A at the end of this session. So in the meantime, I just ask folks who are participating to put your questions in the chat box.

And without further ado, we'll move to the second presentation, "Occupational Contact Dermatitis," by Dr. Pacheco, who is triple board-certified and is professor of medicine in the Division of Environmental and Occupational Health Sciences at National Jewish Health as well as the University of Colorado School of Public Health. And she's the founder and director of the MetALLs program at National Jewish Health, which provides clinical assessment of sensitization to surgical implants.

To you, Dr. Pacheco.

DR. PACHECO: Okay. Can you hear me? I hope?

DR. KASLOW: We can.

DR. PACHECO: Great. All right, let me start sharing. Hopefully this time it works. All right. How about now? Can you see my slides?

DR. KASLOW: Yes.

DR. PACHECO: Yes? Okay. All right. So I've been asked to talk about common causes of occupational contact dermatitis. So what I'd like to cover just in this short presentation is, you know, how you recognize it, if it's possible to distinguish between irritant and allergic contact dermatitis, and to get a handle on what are some of the common allergens that one might find causing occupational contact dermatitis.

So this is the definition. It's an inflammatory cutaneous disease, but it is caused or aggravated by workplace exposures. The picture actually is from a primer from 2015 demonstrating different presentations of contact dermatitis. These are the Mathias criteria and people still use these. I think they're very useful. So the clinical appearance looks like contact dermatitis

and you've been able to identify certain allergens that could be causing it. And that's important. And it gets also to what kind of extracts do we have available to test these allergens?

The anatomic distribution is consistent with the workplace exposure. Meaning if you have someone who says they have occupational contact dermatitis, but much of it takes place under their clothes, that's kind of a clue that that may not be the problem. There is a relationship between ongoing exposure and development of disease. Non-occupational exposures are excluded. Dermatitis improves away from work, but gets worse on returning. And patch testing, which I think is kind of the purpose of this whole symposium, demonstrates positive and relevant reactions.

So why is it a problem? Well, it's common. Obviously my annual costs are out of date compared to the previous speaker. This is from 2010. But if 10 percent of workers report dermatitis, about 7.4 percent had work-related dermatitis, which is at least a million people and

probably much higher now. The issue also, to make the point, is that occupational dermatitis can be caused by irritants or sensitizers, but treatment requires determining the cause.

So most occupational contact dermatitis is irritant-induced and there a list of many agents that are able to cause it. Some of them, even saliva, just constantly licking your lips, chemical burns, water, soaps, solvents. You know, I think painters and mechanics still wash their hands in turpentine at the end of the day because it gets rid of many of the lipophilic agents that they work with. Again, detergents, surfactants, bleaches, polishes, fiberglass, dry cold air. The other point to make here is that if this goes on for too long without identifying the cause, the skin does not return back to normal even if you treat it or remove it from exposure. So there's a certain urgency in making the diagnosis to get some sort of acceptable treatment.

Here are some examples of allergic contact dermatitis and to different chemicals. It

came from a very nice nature review. So A and B are contact dermatitis to hair dye, paraphenylenediamine; C is contact dermatitis to fragrance and lipstick; D is contact dermatitis from shaving cream; E and F are contact dermatitis from the tattoos.

The interesting thing about tattoos is that many of them actually use metal salts for the color. So most blue tattoos have cobalt as the blue coloring, and some of the black tattoos have nickel in them. And because we're working on understanding better presentations in different kinds of skin, I add just a picture of the tattoo of a patient I saw a couple of weeks ago. You can appreciate the fact that it's raised and for him, intensely itchy as a sort of reaction to the components of the tattoo.

All right. Differences. I think part of the problem is that there aren't a huge number of differences. So that's where patch testing and the history become important, because both of them can be red, be swollen, have vesicles, have

oozing. For chronic presentations, you get drying of the skin, hyperkeratosis, fissuring. The difference with irritant contact dermatitis, the edge is limited to the contact area. In allergic, it may be more intense, but it may spread beyond the original contact dermatitis area. I think the thing to note here is that allergic contact dermatitis is itchy, and most people just complain of unbearable itching. It can be a component of irritant, but it's less important.

And then, of course, the time course. So irritant occurs rapidly after the exposure. For allergy, you need some time to develop the allergic response, and then the lesions may not show up immediately, but 24 to 72 hours after exposure, that can make it difficult to identify.

So irritant contact dermatitis sort of opens the door for allergic contact dermatitis. And sometimes I wonder if, because there are so many exposures to irritants, that's what is in part driving the allergic response. But irritants can disrupt the epithelial barrier. They can

activate the first innate immune response, right, the pattern recognition response that then opens a door to adaptive immunity.

So this is from a nice retrospective published in 2022, looking at results from the North America contact dermatitis group and sort of listing the most common occupational allergens. I won't read all of these, but -- because you can group them into certain categories that are very useful.

This, also, sort of has been a graph of what's changed over time. And I think this is pretty interesting in the sense that the carba mix, which is a rubber accelerator, has been increasing in the percentage of positive reactions. The methylchloroisothiazolinone, which is a preservative, is also increasing in frequency, whereas the mercaptobenzothiazole is decreasing. And this is simply, I think, a reflection of where these particular chemicals are used in gloves and as a preservative.

So this is how I cluster these allergens

that I think is useful. So rubber accelerators are probably top of the list. They're in gloves. They're also in safety equipment. And the ones from that list include carba mix, thiuram mix, and diphenylguanidine. Adhesives and glues are very important causes of allergic dermatitis, and partly because they're so reactive. From that list is bisphenol A, a sort of a component of epoxy resins. 2-HEMA is 2-hydroxyethyl methacrylate. It's used a lot in dentistry as an adhesive. And that's kind of a common exposure. Metals, of course, in tools. The big ones are nickel, cobalt, and chromium.

Preservatives are very important. They're used everywhere, in part because the components, say, of shampoo or conditioners or lotions is a very nice, rich mix that bacteria would be very happy to occupy. And so most of them have some kind of preservative in them to prevent bacterial growth, including the isothiazolinones, quaternium-15, formaldehyde, and glutaraldehyde. Lastly, paraphenylenediamine.

It's interesting. It's not just hair dye, but it's used in many other settings to create the dark color, including black henna tattoos.

So same thing from the same paper is what exposures would have been missed if they had not added supplemental extracts? So the North American Contact Dermatitis panel now has 80 allergens. And so looking at their pattern of response, about 82 percent reacted to something in that panel. But 13 percent also reacted to a supplemental allergen associated with their particular occupation. And 5 percent only reacted to the supplemental allergen. And these come from other adhesives, hair dyes, gloves, coatings, moisturizers, and metal working fluids. So the kind of points to the area saying that there are some allergens we need a better supply of in order to make the right diagnosis.

I thought this was kind of interesting. It looks at the top sensitizers in different countries. So these include Europe, then Germany, Austria, and Switzerland, Greece, USA, Australia,

and Singapore. And I think if we're just looking at the USA, you can see that nickel, again, remains the highest. Fragrance mix is important. The methylisothiazolinone is important. Formaldehyde in the U.S., balsam of Peru, MCI, and cobalt as well. But there's some that seem to be less prevalent in the U.S., such as colophony, potassium dichromate, and the like. But it just suggests that there are different patterns of important allergens in different countries. So to make the diagnosis you need location, history, and timing. And the location is the first very important clue.

So looking at the picture of the hands, it's clearly a contact dermatitis, probably related to gloves. The picture on the right suggests this is an airborne exposure because you have the rash on the V of the neck that may be exposed as well as the face. I won't go into great detail here, but I really like this table showing the different patterns that you would get based on the nature of the exposure. I mean,

airborne contact dermatitis is going to be different, right, from face cream contact dermatitis. Periorbital may be related to things on the hands or on the skin. And then there's also personal protective equipment contact dermatitis.

So onset with latency takes time to develop the reaction, association with a specific task. You identify the cause by patch testing.

So I'm just going to -- since I was asked to talk about occupational dermatitis, I'm just going to briefly review some of the common allergens. So in terms of agriculture, you're really talking about metals. Some of the pesticides are sensitizers, including -- oh, no, I forget. Well, anyway, rubber additives for the gloves, thiuram mix. And there's also exposures to plants, animal feed, and fish that can cause a contact dermatitis.

In construction workers, again you get exotic woods can cause contact dermatitis. Chromium is a component of cement; colophony,

which is an adhesive used by electricians; plumbers, acrylates and epoxy resins. So the other important point to make with construction workers are the waterproofing chemicals because these are isocyanates and they can cause both the contact dermatitis as well as occupational asthma.

Healthcare workers and housekeeping. I think this is almost one of the largest category of workers that we see given the common exposures to rubber accelerators, the preservatives and disinfectants, the adhesives are important. Similarly, the housekeeping personnel have similar exposures. But I think some of the top ones on my list are the bacterial enzymatic cleaners because these are enzymes taken from bacteria, ethylene oxide, and I think quaternary ammonia compounds is really important. They're used in many kinds of disinfectants, surface disinfectants. People like to use them because they don't smell like chlorine, but they're important sensitizers in that occupational group. Similarly in housekeeping, though, there are many irritants

that make the top of the list and fewer sensitizers.

I put this up just because it's important to realize that these things are everywhere. So I simply looked at the safety data sheet for Simple Green, Lysol Disinfectant Spray, and Mrs. Meyer's Clean Day Multi-Surface Everyday Cleaner. And I've underlined the sensitizers that are present in these different products and they include some plant products, citrus, lemon, lemon peel, but, again, preservatives, isothiazolinone. Lysol Disinfectant Spray is disinfectant because it has a fairly large amount of a quaternary ammonia compound along with some pretty good solvents, including ethanol. And then lastly, this Mrs. Meyers Clean Day cleaner, again, has the same preservative, methylisothiazolinone, as well as fragrances. So these things really are ubiquitous. The point to remember here is that green cleaners are green for the environment, but they're not necessarily green for the person using them.

Hairdressers, cosmetologists have a lot of allergens that they're exposed to. Again, permanent hair solutions, hair bleaching, hair dyes, paraphenylenediamine, hairdresser tools, I've seen much less of that. But nail technicians also are exposed to a number of really important sensitizers, especially the acrylates. So these are just pictures of someone reacting to nails; contact dermatitis around the eyes.

Mechanics, also. Remember that metal working fluids used to be only made of water. Now it's a combination of petroleum products and water. And all of them have biocides to prevent growth of both bacteria and fungi in them. But these are sensitizers.

All right. Plant allergens and florists. Interestingly, right, florists, outdoor workers, and food service workers are often exposed to the same plant allergens. Peruvian lily and its relations, including onion and garlic, are a common cause of contact dermatitis. For those of us who have reacted to poison ivy in

an exuberant way, I include the leaves of three. Let them be up there. But food surface workers are exposed to many different allergens as well. I've listed some of these here. Remember, mangoes cross react with Rhus toxicodendron. There are lemons and limes. They're antimicrobial chemicals and physical conditions as well.

Patch testing is the key to treatment. And so expanding on what Dr. Ehrlich commented on earlier, this is a nice set of pictures showing the different grades of patch test reactions. So A is doubtful; B would be considered 1 plus; C 2 plus; D, three plus, where you get weeping and vesicles; E is kind of a shiny irritant (inaudible); and then F and G, there is also an edge effect that it can also be caused by irritants or by analogy to topical steroids. So it's more concentrated in the center so you get less of a reaction, but you do start to develop a reaction around the edge.

So here's the take-home message. Most occupational contact dermatitis is irritant

induced by water, solvents, and surfactants. Allergic occupational contact dermatitis is characterized by latency, takes time to develop the immune response, and itching. Location, history, and timing will help you focus what allergens are probably important. There are some common allergens. Patch testing is the key. But there are also some allergens out there that we either have very limited knowledge of or limited patch testing reagents.

And that's it. Thank you very much.

DR. KASLOW: Thank you for your review of the breadth of allergens, the clinical presentation of diagnostic approaches to occupational contact dermatitis, and really, you know, the differentiation from irritant contact dermatitis, and finally the role of patch testing and expanding availability of those patch tests.

Again, please submit questions that you have in the chat box. And we will now move to the "Economic Burden of Allergic Contact Dermatitis" by Dr. Chen, who's a clinical professor at

Stanford University School of Medicine with an interest in allergic contact dermatitis and atopic dermatitis. She's the past president of the American Contact Dermatitis Society and has also served on its board of directors.

So to you, Dr. Chen.

DR. CHEN: Thank you. See if I can make this work. All right. So thank you for inviting me to speak today. I am going to be talking about the economic impact of allergic contact dermatitis in the United States. As an overview, I'm going to start out with some background. I'll talk a bit about the cost of contact dermatitis as well as the rising cost of missing allergic contact dermatitis. And then I'll finish up with speaking on the cost benefits of patch testing.

For background, contact dermatitis is the fifth most common diagnosis seen by dermatologists and it accounts for up to 90 percent of all occupational skin disease, as you just heard from those last two great talks. Up to 20 percent of the general population are thought

to have skin allergies that could result in allergic contact dermatitis, so it's extremely common. And allergic contact dermatitis has been associated with many comorbidities. In the infectious category, it's been associated with increased rates of impetigo, cellulitis, cutaneous abscess, cutaneous candidiasis, and HSV. In the psychiatric category, it's been associated with increased rates of depression, anxiety, ADHD, and psychiatric medication use. And in the sleep health category, it's been associated with increased rates of insomnia and daytime somnolence.

So it should come as no surprise that allergic contact dermatitis can be associated with a significant economic cost. And these can be broken down into direct costs and indirect costs. Direct costs include medical appointments, diagnostic procedures, medications, hospitalizations. Indirect costs include things like lost productivity, absenteeism, job change, or disability.

So what are the costs of allergic contact dermatitis? I wanted to start out with this case series from Lidden, et al. This is an older study, but I think it demonstrates nicely the potential cost of allergic contact dermatitis. The authors in this study wanted to evaluate the impact of allergic contact dermatitis to toluene formaldehyde sulfonamide resin, also known as tosylamide/formaldehyde resin, which is found in fingernail polish. And this is a pretty uncommon allergen.

The authors wanted to look at the impact of this allergy on their patients. They found that 18 of their patients had patch tested positive and presented with face, neck, and hand dermatitis. And you might be thinking to yourself, what's the big deal? It's just allergic contact dermatitis to nail polish. But until the correct diagnosis was made, 11 of the 18 patients actually went on sick leave or stopped working, 4 required hospitalization, and 2 of those patients subsequently lost their jobs. Nine were on sick

leave for two weeks to seven months. Two even stopped working at their computer terminal out of a mistaken belief that that was what was causing their rash. So you can see even in milder cases, productivity was affected. And most importantly, all of these cases resolved within a few weeks once patients started allergen avoidance after they had gotten patch testing and learned what was causing their rash.

So what are the actual numbers associated with the cost of contact dermatitis? Unfortunately, our data is a little bit limited in the United States, but this is probably the best study that has been published on the topic. This was from the 2004 Burden of Skin Disease Project that was conducted by the American Academy of Dermatology Association and the Society for Investigative Dermatology. They looked at a number of national, private, and publicly available databases, which you can see listed here in that third bullet point. And what they found was that contact dermatitis was the fourth most

common skin disease seen by dermatologists in 2004. It was the fifth most economically burdensome skin disease.

And they calculated a total direct and indirect cost of $2.2 billion, which would be the equivalent of about $3.8 billion today, adjusting for inflation. And this was their breakdown of the costs. So the direct cost was calculated to be about $1.6 million. The indirect cost because of lost productivity was calculated at $566 million for a total direct and indirect cost of 2.2 billion, like I mentioned on the last slide.

The authors also did try to calculate the intangible costs due to quality of life impact. They did that based on existing literature. And the number that they calculated for contact dermatitis was a cost of $1.9 billion for a total cost for contact dermatitis of $4.1 billion in 2004, which would be the equivalent of about $7.2 billion today.

On this lower table, you can see the direct cost breakdown. So you can see the

majority of the cost came from prescription drug costs as well as office visits. There also was a significant contribution from hospital emergency department visits and hospital outpatient visits, and then, to a lesser extent, hospital inpatient stays as well. Here on the lower table you can see the indirect costs by category. So you can see the majority of the indirect costs came from lost work days followed by restricted activity days and then caregiver lost work days.

This was a follow-up study, the 2016 Burden of Skin Disease Report, also conducted by the American Academy of Dermatology. In this study, they looked at a number of claims databases from insurance enrollments and claims databases. And so they looked at the year 2013. You can see listed here all the databases that they looked at. And what they found in this study was that 84.5 million Americans, or about 1 in 4, were impacted by skin disease in 2013. Contact dermatitis was the fifth most common skin disease and it was among the top five skin diseases causing lost

productivity.

They estimated the cost at greater than $1.5 billion in medical treatment alone. This actually surpassed the cost of treating melanoma skin cancer. And they estimated the cost at 700 million for lost productivity. So in today's dollars, that would be the equivalent of medical treatment costs of $2.1 billion and lost productivity costs of $980 million.

This is another study from Blanca 40 looking at the burden of contact dermatitis in U.S. workers. They looked at the 2004 Medical Expenditure Panel Survey household component data and they included patients who were age 16 to 65 working in 7 industry sectors. And this is their breakdown from that study. The total direct and indirect cost came out to be about 1.2 billion, which would be the equivalent of 2.1 billion adjusted for inflation today. Direct expenditures were calculated to be at about 550 million, indirect at 625 million, which would be the equivalent of 964 million and 1.1 billion today.

The per person expenditure was calculated to be about $552 per patient, which adjusted for inflation would be about $965 today.

You might be noticing that the indirect expenditures are pretty similar for this study compared to previous study also looking at 2004 I showed you a few slides ago. The direct expenditures for this study were quite a bit lower than that previous study and this could be due to several reasons. This is a survey-based study. So medical expenditures were calculated from patient recall of their medical expenses and that, of course, is subject to recall bias. Also, the authors were only looking at this one subset of patients age 16 to 65 in those 7 specific industry sectors. So this was not representative of the entire U.S. population.

They did go on to break down the cost by industry sector. So you can see by far and away the highest cost was associated with the service industry, where the total cost in 2004 amounted to be about 844 million. So the service industry,

you know, think healthcare workers, hairdressers, cleaners, restaurant workers, and so forth, so definitely hit hard by contact dermatitis. The second most costly industry sector was construction, followed by wholesale and retail trade and then manufacturing.

This is another study looking at occupational contact dermatitis. Looking at Oregon from the years 1990 to 1997. This was a retrospective analysis of workers' compensation claims. The mean cost per claim was about $3,500 and the highest total costs were associated with precision production and crafts, which averaged to be about 8,000 per claim, and wholesale trade, which averaged to be about 7,000 per claim. And the total cost was $2.2 billion for these 8 years in this one state, averaging about $271,000 annually. And this would be the equivalent of a total cost of $3.9 billion today, or about $474,000 annually.

Note that this is probably an underestimate. The Oregon Workers Compensation

database does not include patients who are self-employed. And we know that there are certain occupational subgroup groups that are heavily affected by contact dermatitis, but are often self-employed, such as hairdressers, for example. So, again, this is probably an underestimate.

So let's talk limitations. Any time we're looking at any studies evaluating cost of contact dermatitis, I think presenteeism is a huge factor where patients still show up to work. Maybe they're feeling well enough to still show up to work, but their productivity may still be taking a hit. And it's hard to quantify that. Also, milder cases are unlikely to be reported. Job loss is difficult to capture, as well as underreporting of occupational cases due to fear of job loss.

Access to healthcare, of course, is a huge issue. If they don't have access, we can't quantify the costs of them seeking medical care for their condition. It's also hard to capture the cost of adverse effects of unnecessary

medications. The cost of over-the-counter products is also hard to capture and that is likely significant since most of our contact dermatitis patients do reach for over-the-counter products first whenever they develop contact dermatitis. And you saw from these previous studies I showed you, it also is hard to calculate the cost in terms of quality of life and lower standard of living. So definitely all of these studies are going to be underestimates.

So I wanted to spend the next few slides talking about the rising cost of missing allergic contact dermatitis. One of the things that's tough about allergic contact dermatitis is that it has to be distinguished from a lot of other conditions. And probably one of the most difficult things to distinguish it from is other forms of eczema because the appearance may be exactly the same among different forms of eczema, but the causes and treatments often differ. And the costs are significantly higher now, likely, than prior to 2017. Since 2017, we've had an

explosion of much improved, but costly treatments that have been FDA approved for other types of eczema. So these have been huge treatment advances. But, again, they are associated with a price tag.

So a prime example of this is atopic dermatitis. This is a form of eczema that affects about 13 percent of the pediatric population and 7 percent of the adult population in the United States. Atopic dermatitis may be misdiagnosed as allergic contact dermatitis because they may look exactly the same. Also, atopic dermatitis may coexist with allergic contact dermatitis and studies show that about 50 to 66 percent of patch tested atopic dermatitis patients will have one or more patch test positives.

Why does this matter? It's because the management differs. So, allergic contact dermatitis, as you've heard, we manage this with allergen avoidance, primarily. Atopic dermatitis, on the other hand, is a chronic disease that typically requires ongoing medication

indefinitely. And so I've included here the atopic dermatitis medications that have been FDA approved since 2017. These are the annual retail costs, and you can see in bold here, these are the systemic agents and the cost ranges from 40,000 to 130,000 per year. Down here at the bottom of the slide, unbolded, these are the topical agents that have been FDA approved for atopic dermatitis since 2017. And you can see here, even for these top agents, the annual cost ranged from 13- to 30,000. So, clearly, there's a steep price tag if we miss allergic contact dermatitis.

So in our last couple minutes, I wanted to also touch upon the cost benefits of patch testing. This is the most recent study on this topic, actually hot off the presses. The manuscript is currently under review and the data has been presented already at national meetings. The study looked at claims data from the Merative MarketScan Research Data Set [sic], which is a database for commercially insured patients. And the study included about 6,600 patients who had

undergone patch testing in 2015 and had been given a diagnosis of atopic dermatitis and/or contact dermatitis.

And you can see here the data for the direct cost of outpatient care one year before and one year after patch testing among these patients who had been patch tested in 2015. So across the whole cohort, the direct cost per patient was a median of $545 per patient in the year prior to patch testing and in the year following patch testing, this cost had dropped down to 279 per patient. And this was statistically significant.

There were similar findings across all subgroups, including patients who had only been given a diagnosis of atopic dermatitis, patients who had only been given a diagnosis of contact dermatitis. And the greatest cost savings were actually seen in patients who were given both a diagnosis of atopic dermatitis and contact dermatitis. So the direct cost per patient for that subgroup was actually $850 in the year prior to patch testing and it dropped down to 426 in the

year following patch testing.

And it's important to note that this study period was 2014 to 2016. So this actually predated all of those much more expensive targeted atopic dermatitis treatments that I just showed you a couple slides ago. So we expect the cost savings to be even higher in the current climate.

So this is the inpatient data looking at patients who were hospitalized with specifically the primary reason for hospitalization being atopic dermatitis or contact dermatitis. This was a very few number of patients out of the whole cohort, but you can see that the average cost per patient was about 8,000 to $9,000 per patient, and that none of the patients required hospitalization for these conditions in the year following patch testing. So this does support cost savings with inpatient care as well.

So takeaways from this study. Patch testing was associated with significant cost benefits. Outpatient cost savings, interestingly, in this study were mainly due to a reduction in

the expenses associated with office visits for dermatitis. So, like I was mentioning, we do expect that we'll see further cost savings in this current era of newer and more costly eczema medications, and further studies are ongoing looking at that. Overall, this study suggests that successful timely identification of contact allergens is an effective and cost-efficient intervention for patients with dermatitis.

So in conclusion, allergic contact dermatitis is associated with a significant economic burden. Patch testing allows for the identification of potential culprit allergens and is associated with significant cost savings. And future studies are required to better understand the full economic impact of allergic contact dermatitis.

So with that, I'll thank you for your attention. I think we're taking questions in a few minutes.

SPEAKER: Dr. Kaslow, you're muted.

DR. KASLOW: I guess we have to do them

both. Sorry. Okay. So I'll start off. I'll thank you again, Dr. Chen, a great summary on the economic burden of ACD, both its indirect and direct costs of this fifth most common skin disease.

We will move on now to a pediatric topic, "Contact Dermatitis in Children." And we'll turn to Dr. Jeff Yu, who's a double board-certified adult and pediatric dermatologist specializing in ACD and atopic dermatitis, and he's currently the chair of dermatology at the Virginia Commonwealth University, where he leads the Contact Dermatitis and Atopic Dermatitis Clinic and is the president of the American Contact Dermatitis Society.

To you.

DR. YU: Perfect. Thank you. Everybody can see the screen? Everybody can hear me okay?

SPEAKER: Yes.

DR. YU: Perfect. All right.

DR. KASLOW: Yes.

DR. YU: Great.

DR. KASLOW: We see the PowerPoint.

DR. YU: Thank you. So, again, thank you all for giving us the opportunity to talk to you all about the importance of allergic contact dermatitis in diagnosing and treating our patients who suffer from this condition. And one of the areas that I am focused on in my clinical practice is looking at allergic contact dermatitis in children, what I consider a particularly susceptible, but also important population to consider because a lot of these kids, like what Dr. Chen and people before me have, you know, briefly discussed, is that the prevalence of atopic dermatitis is high, but certainly not every kid that we think has eczema just has regular run of the mill eczema.

And sometimes patch testing can really end up being steroid as well as systemic medication treatment sparing, not only saving U.S. Healthcare dollars at the end of the day, but also saving these kids from a lifetime of one of these therapies, which can be made unnecessary,

especially if we are able to have access to the types of patch test allergens that we need as well as the patch test series that we currently use. So I'm really hoping that through this presentation you all will understand the importance of patch testing in children and making sure that we have access to these medications or these materials here.

We're going to talk a little bit about the existing data on the prevalence of ACD in kids. We're going to talk about how to patch test kids from different work groups that have been published not only in the U.S., but around the world. And then on the very end, I want to present two cases of successful patch testing in children that led to clearance of their dermatitis and rash.

So one of the questions I often get asked from my colleagues is whether or not kids actually get allergic contact dermatitis. This is a study that was commissioned by the American Academy of Dermatology that shows that kids, those

between the age of 0 and 17, about a third of the population had contact dermatitis of some --

DR. KASLOW: Excuse me, Jeff.

DR. YU: Yes.

DR. KASLOW: I don't -- we don't see your slides advancing and you may want to also put it into presentation view.

DR. YU: Okay.

DR. KASLOW: You know, click the little, you know, easel thing below.

DR. YU: Okay. I am sorry about that, guys.

DR. KASLOW: It's all right.

DR. YU: Let me try this one more time. I apologize.

DR. KASLOW: I think if you go -- yeah, I think if you go into PowerPoint and you go Share on Teams, I think that works. That's one way to do it or to do the share. But for some reason it wasn't advancing and it wasn't in presentation mode.

SPEAKER: We can pick up share, if

needed, Dr. Yu.

DR. KASLOW: Yeah, maybe you guys go ahead and do that because I think that might actually be easier instead of me kind of putzing around here. Great. Okay. And I can't control it, right? There's no way for me to control on your end. Okay.

SPEAKER: Correct.

DR. YU: Okay, perfect.

SPEAKER: Please just say, next slide.

DR. YU: Let's do that. Okay. Next slide, then. So this was the graph that I was referring to with the study that was commissioned by the American Academy of Dermatology that showed about one-third of the kids can develop contact dermatitis. And certainly contact dermatitis is not lost in adults. About 1 in 4 to 1 in 5 adults also develop allergic contact dermatitis. Next slide, please.

And one of the reasons why we think allergic contact dermatitis maybe didn't occur in children is because of the predominance of atopic

dermatitis, which we now know very well is a Th2 predominant type of disorder versus, historically, we used to think allergic contact dermatitis was very much Th1. And our understanding of the immune system at least, is that if Th1 is overexpressed, Th2 is then underexpressed, and vice versa is also true. But now with a lot of the more recent data, we know that is not the case. Next slide.

So in studies that were done, and one of these studies was done by our very own Dr. Belsito here, it was his group found that more kids who had atopic dermatitis had more positive patch testing reactions to one or more allergens. Meaning not only are kids with atopic dermatitis likely to get allergic contact dermatitis, they were then more likely to have more positive reactions on patch testing and, therefore, more likely to suffer from ACD. Next slide.

And in a study that was done in India, they found that the more severe the atopic dermatitis, so higher the SCORAD numbers were for

these kids, the more likely they were to have positive patch testing as well. Next slide.

And studies that were done by the North American Contact Dermatitis Group between 2001 and 2008, looking at roughly 2,000 kids, found that even though kids have a higher prevalence of atopic dermatitis and a higher prevalence of asthma, they had a similar rate of allergic contact dermatitis compared to their adult cohort, as well as a very similar patch testing rate. Meaning that kids can absolutely get allergic contact dermatitis and should be routinely evaluated for ACD, especially if the clinical suspicion is there. Next slide.

And these are just some photos from a continuing medical education article that I wrote with some of my colleagues looking at patch testing that can happen in children. And certainly even kids as young as five years old, for example, as this little boy can easily fit 80 allergens and perhaps even more if we expanded to some other sites, just showing the importance and

the ability for us to comprehensively patch test children. Next slide.

And this is a picture of a child that was about 16 to 18 months of age where we were also able to patch test this child with a much more limited yet important select series of allergens. Next slide.

So I believe patch testing is extremely important in children. And I wanted to show that patch testing actually made an improvement in the kids dermatitis. So between 2017 and 2022, we looked at roughly 166 kids that were patch tested at our center. Fifty-one of them had follow-up data and we found that about 27 percent of them improved completely after patch testing. So this is without other interventions, without topical medication.

What we did was that we patch tested them, told them what they're allergic to, gave them guidance in terms of good skin care and avoiding some of those allergens, and then about 27 percent of them had 100 percent improvement in

their dermatitis. No rashes, no topical, no systemic medications needed. Fifty-five percent of those kids partially improved to various degrees, but the vast majority of them also had atopic dermatitis. I never tell kids that we're patch testing you to cure your atopic dermatitis. We're patch testing you to remove the allergic contact dermatitis component. You're probably still going to have some atopic dermatitis left over if you're somebody that suffers from both, which many of these kids did. But about 55 percent still improved partially.

What that could mean is that maybe these kids no longer needed daily topical steroid use. Maybe these kids went from somebody that needed a systemic biologic medication to maybe just using topical or moisturizing on its own, still providing a significant quality of life as well as a medical benefit to them just by patch testing alone, a test that has been shown to be very safe and very effective. Unfortunately, about 17 percent of those kids did not improve at all. And

again, the vast majority of them had atopic dermatitis. Perhaps those kids were more of your pure atopic dermatitis kids with no allergic contact dermatitis versus the vast majority of them that had improvement had some degree of allergic contact dermatitis. Next slide, please.

And what were some of the top allergens that we found? I'm just showing some arrows here with some of the fragrance chemicals being some of the top hitters. We had metals, we had preservatives, and then we had some of the other excipients that you can see on this list. All these allergens are things that we can find in daily products that are included in your shampoos and your over-the-counter topical medications, in your jewelry, in your toys. These are all commonplace everyday allergens that we are using to patch test. And therefore, that kind of talks a little bit about the safety of the patch testing when we're putting these on kids.

There is no evidence of active sensitization for any of these allergens. And

kids do react with these with a very mild local reaction that usually manifests with some degree of itching. But we're able to find with pretty good sensitivity as well as reliability that these were positive reactions and hence avoiding them led to significant improvement in the vast majority of these kids. Next slide, please.

So what does this all mean here? Pediatric patch testing is important, as I've hopefully have already shown you here, and should be considered a routine evaluation for dermatitis, especially if they are not just your regular atopic dermatitis or presenting like regular eczema. And kids who have atopic dermatitis are not only likely to develop allergic contact dermatitis, but more likely to develop it, especially if it is a more severe variant. Next slide, please.

So what are some of the working recommendations for patch testing in children? And I don't think the U.S. is really unique in patch testing kids because in other parts of the

world, especially in Europe, they have multiple recommendations that are published for how we should be patch testing children as well. Next slide.

This is a position paper from EAACI, which is the European asthma and allergy group there. And they had some recommendations for patch testing in children. They had baseline series that included about 10 allergens and additional allergens that are recommended, especially depending on their clinical history, as well as allergen exposure that is shown here. Next slide.

We published a pediatric baseline series here in the United States back in 2018, recommending a panel of 38 different allergens that has roughly a 70 percent detection rate for the top 10 allergens in children, as we've shown in studies. And this panel should be used in children, especially if they're not big enough or old enough to accommodate the standard series that we use, such as a North American 80 or the

American Contact Dermatitis Society 90 core series. Next slide.

And then there's also a current proposal going around from the European Society of Contact Dermatitis looking at contact allergy in children. And they are proposing an 18 allergen baseline panel for kids with a further 7 recommended additions, making a total of 25 allergens that they recommend patch testing all children for at minimum. And this is a group of multiple different countries, including Belgium, Italy, Spain, and such. Next slide.

This is the study that I was referring to earlier, looking at how different patch test series are able to capture the top 10, 20, or 50 allergens in children. You can see on the left-hand panel here the pediatric baseline series, about 70 percent detection rate for the top 10 allergens. What I tell people, though, more is always more when it comes to patch testing, right? If we are only using a small set of allergens, there is a very high likelihood of

us missing important allergens here. So you can see the pediatric baseline series has 38 different allergens. Then if you look at some of the other series here of 60, 70, or 80 allergens, the detection rate for the top 10 allergens incrementally goes up to the point where the North American Comprehensive 80 includes 100 percent of all top 10 allergens can be detected there. Next slide.

So now what does this next part mean? Different regions use different allergens due to exposure differences. Certainly our exposure here in the U.S. is a little different than the exposure they have in Europe. Nonetheless, both groups or both continents certainly believe that patch testing in children is important enough for us to go about and make these baseline series and these baseline recommendations. And I think there is a growing international interest in established baseline series in children. I know that in Asia they're working on something and in the Australia, New Zealand area they also have something similar

for kids, too. Next slide.

So what are some cases of pediatric patch testing that I have seen that have made a big difference in the kids lives? First -- next slide.

So here is a 12-year-old atopic child who has a 4-year history of hand dermatitis that got worse during 2020 to 2021. So remember, this kid has a history of underlying eczema, but the hand is a new involvement and that is the prerogative for us for patch testing here. There were no significant changes in activity, had some bacterial hand infections that so often happened with hand eczema and it was successfully treated with cefalexin. Next slide.

Here are some photos of the kid's hands. You can see those fissures that are very painful. You can see the scaling that involves both the dorsum as well as the palmar surfaces of the fingers and the palms, too. Next slide.

So the diagnosis here from patch testing was an allergen called methylisothiazolinone. And

this has been referred to already earlier by my colleagues. But this has been a top hitting allergen really since 2011. And currently it's the number two most common allergen in both adults as well as children. And when this is positive, the allergen has the highest degree of relevance when we're looking at the data here. So if somebody is allergic to this, there's a very good likelihood that there is a product or an exposure that the patient is being in contact with that is leading to their contact dermatitis.

Where can you find methylisothiazolinone? We find it in personal care products, shampoos, conditioners, for example, different paints that we are currently using to paint the walls, cleaning supplies, nail polish, slime, for example, that kids all play with. So this is a very popular type of preservative that industry is using in a lot of their products. And we're fortunate to be able to test patients to this allergen because if we didn't have this, then we really would be missing

the number two most common allergen in adults and kids and, therefore, preventing them from healing and recovering completely. Next slide.

So now the search really begins. We really have to figure out where this exposure is coming from. So we kind of went through all of his products at home with his mother. And then the only hand soap, the only new thing that they had was that hand soap that they bought. And then this hand soap included the methylisothiazolinone that you can see on the very bottom of the page here. Next slide.

All right. Case number 2 here, my last case, this is a 15-year-old male with a history of type 1 diabetes and for the last year has been using a continuous glucose monitoring system, the Dexcom G7. Ten days after starting the Dexcom, he developed this rash that you can see here in this photograph at the site of the Dexcom placement. Mom has tried a lot of different over-the-counter barrier tapes and different types of bandages, and all of that has had very limited efficacy. So he

came in for patch testing. Next slide.

We patch tested him and he was found to have colophony allergy as well as some of these other adhesive allergies. Next slide.

And he had an acrylate panel that was there for negative. Next slide. So looking at the different types of glucose monitors that we have, now a lot of these are not publicly available information. Right? This is where clinical studies really come in handy in having a spectrum of allergens that we can potentially test patients to be really useful. Because these companies come out with these adhesives and these sensors with these various different types of allergens. And some of these are not readily available allergens, some of these are not things that we might have ever heard about before.

One of these allergens here is something called isobornyl acrylate that really came to our attention about five, six years ago when we started finding it in the FreeStyle Libre. And since then we've really seen an epidemic of people

being allergic to this allergen. And I think having the nimbleness to say we are going to test for this allergen now because it's an emerging allergen, that's the only way that we're really going to find whether or not somebody is allergic to these allergens.

But having the ability to test to all of these things really allows us to say, well, you are using this sensor and, therefore, we can test you to this allergen and that's prove that this allergen is the problem. And then let's switch you to something else because we're able to say you're negative to these allergens, too. And this really leads to a significant positive quality of life outcome, as well as control of their diabetes. Because so many people now rely on these sensors and insulin pumps to be able to kind of control their day-to-day blood sugar.

But looking at this list here, you know where is G7, right? Where is the Dexcom that he is using? Certainly it is not on this published paper. So now we have to figure out what's in the

G7. So next slide.

So this, fortunately, this paper that came out in 2024 looked at and analyzed the different types of adhesive chemicals that was in the G7 and they found not only isobornyl acrylate, or IBOA there, which we tested him for and he was negative, He actually had colophony which we also tested him for and he was indeed positive. Really leading us to say, well, that is really the culprit allergen. G7 is your problem and let's switch you to a different glucose sensor and then see what happens. Next slide.

So what does this all mean now? So the more allergens that you test, the more likely you are to get a relevant positive result. Because if you don't know what they're positive to, you're really not going to be able to figure out what to test them to and really not going to be able to figure out how to get them to avoid that. And patch testing is potentially life-changing in children. And hopefully, from this presentation you all have gained an appreciation for how

important it is for patch testing evaluation in this population.

Thank you all very much.

DR. KASLOW: Great. So thank you, Dr. Yu, for bringing the pediatric considerations in patch testing for ACD and the importance of actually distinguishing between and differentiating from atopic dermatitis.

Before going to our panel Q&A, I think we are going to have a couple -- or video testimonials of the patient experience. So I will turn it back to Corey.

MS. BERNARDONE: So my name is Madeline Meyer Bernardone (phonetic). I suffer from contact dermatitis. I had my first allergic reaction late last year and I had this recurring rash all over my face that was red and bumpy. And I wasn't sure exactly what was causing it and it affected my life quite significantly. I'm a professional. I am in court multiple times a week. I have to look professional. And a lot of times that comes with wearing makeup. And when

you're having this rash all over your face that you don't know what's causing it, it made me, you know, hesitant to wear makeup, hesitant to be in front of people. So I knew that I needed to get assistance for it.

I first went to my normal cosmetic dermatologist that I was seeing for melasma and I showed her pictures of my face and I was just told that maybe I was using products that were too abrasive and that I needed to just kind of pare back on that. I knew about a dermatologist at Mayo Clinic that specialized in allergens and sent him some photographs of my face. And right away he was like, that's eczema, that's contact dermatitis, and you should come in for patch testing to figure out exactly what you're allergic to.

So I first came in for the patch testing, I think summer, earlier summer of this year, and I did the full panel on my back and I think I did the subset as well for the less common allergens. And came back that several products

that I was using were likely the cause of the rash that I had on my face. And I was able to learn exactly what I was allergic to and then figure out what products that I needed to avoid.

In doing that I have not had a rash on my face since I did the patch testing. I know exactly what products to avoid and it's really positively affected my life in quite a dramatic way to know that all of a sudden I'm not just going to have a rash all over my face. So I'm really grateful that I was able to go through the patch testing process.

And I think the most important takeaway from patch testing is it's something that's really necessary because there's so many ingredients and products now, it's really impossible to just try to eliminate all of your products and start back up one at a time. That wasn't possible for me. Like I said, I need to wear makeup, I need to look professional. So this gave me a way to find out exactly what I was allergic to, avoid it, and then start to select products that weren't going to

cause this rash.

MR. NIMJEE: Good afternoon. My name is Shahid Nimjee. I'm a vascular neurosurgeon. I'm giving this testimony as it relates to my experience with patch testing as I received it more than a decade ago to deal with lesions that were coming up on my hands. It was inhibiting me from comfortably doing my job. It was causing what I found out later was eczema and inflammatory lesions on both my hands and going up my arms. And we didn't know what it was.

Thanks to patch testing, I learned that I have a rubber accelerant allergy that was likely acquired in the course of wearing surgical gloves for so many years. And then in addition to that, wearing gloves during my Ph.D. before that. The patch testing allowed me to get appropriately diagnosed. It then allowed me to find alternatives that to this day I use in the OR to operate on patients and fulfill my responsibilities as a surgeon. And I'm very grateful for the availability of such a service to

allow me to keep doing what I do today. Thank you.

MS. ERTEL: My name is Eva Ertel. I am from Buffalo and I have a longstanding history of contact dermatitis, also known as eczema. I have had a longstanding issue with eczema since I was around two years old. It's gotten worse since I was five years old and I'm still dealing with it to this day.

When I first started feeling the symptoms of eczema, I went to a lot of pediatrician doctors, various different doctors, including different allergists, and all of them were very consistent with giving me a gluten allergy diagnosis, a milk allergy diagnosis, and they all ended up being prognoses because I was not able to find out what my real allergies were until I was able to get patch tested.

Between the time that I was patch tested and the time that I have been in contact with different doctors, many of them prescribed more antihistamines, topical and oral steroids rather

than giving me the suggestion of getting patch tested. It was only until about 2015 when I was able to meet with Dr. Susan Nedorost. She worked at Case Western University in Ohio, and I was able to get patch tested by her. And I found out that I was allergic to lauryl glucoside, vitamin E, and propylene glycol. And by using the elimination diet for my food and eliminating all the products out of my reach, whether that being makeup, lotions, or food, like I mentioned, I was able to be clear within 18 months. And for the past 10 years I have been clear of eczema with the occasional flare-up.

Within the past year I've had a six-month long flare-up and I had burning rash same as it was when I was a kid. It felt like my whole fire was on -- my whole body was on fire and I had hives everywhere. I had raw burning skin to the -- it was hot to the touch and I was continuously inflamed. I was not able to feel comfortable in my own skin. And for a long time it debilitated my mental health.

And I went to see other doctors and allergists within those six months and they prescribed me the same topical and oral steroids that have a big part of the allergy that I'm allergic to, which is propylene glycol, and I was not able to take those. And so I went to get in contact with my previous dermatologist from Ohio, Dr. Susan Nedorost, and she was able to repatch test me again. And I found out that I was allergic to six different allergens.

And patch testing has really changed a lot of my perspective within my lifetime because whether I get jolted or told to take oral steroids or take antihistamines, I know that with my past experience I've been able to find out my allergens through patch testing. And a lot of different doctors 10 years ago and up to this day where I've had another flare-up in the past six months, that many dermatologists, allergists, or regular doctors will guide me to the route of taking different medications instead of getting patch tested. I think that patch testing has really

affected the way that I am able to freely live my life without much eczema to this day. And I believe that it's super, super important. And not many people know about it from different stories of eczema that I've read online or talked to.

And I really appreciate being able to not have to take a long-term steroid. And I'm able to eliminate any of my allergens from my diet, whether that's propylene glycol or my most recently found allergies, which is gold, lauryl glucoside, decyl glucoside, pivalate 21, which is a class of steroids. I'm actually allergic to a class of steroids, which I wouldn't have known if not for the patch testing, which is really life detrimental. And if I were to have a serious medical emergency, I would have had a systematic reaction to that specific steroid.

So eczema still impacts me to this day because I currently have to worry about steroids and whether those are being used for my skin for an occasional flare-up or for any medical emergencies that I may have. And I think that

it's just important to continue to speak about patch testing and to bring that knowledge into focus for sure.

And like I said, eczema still impacts me to this day. I still have to read labels every day. And there are about 20 different analogous names for propylene glycol like propanediol, methylethylene, and PPG-dash-a certain number. And it's very hard to explain to an average person that may not deal with this. So I'm grateful for the knowledge that patch testing has gave me and I wouldn't have it any other way personally.

And I still have the occasional environmental flare-up every once in a while, but it's very detrimental to my mental health, my sociability, and whether I feel comfortable in my own skin. So I think it's important to really bring patch testing into a wider scope and that I really find it's important to fix what you can with different types of medicine, whether that's Western or holistic. And wherever patch testing falls, I find that it's super, super important to

take that route and it could be solvable or at least lessen your symptoms, which for me were horrible personally. And I really appreciate that as an option. And I will continue to advocate for patch testing for other people who may deal with eczema, whether that's a younger kid or an older adult. I think it's just important to have that knowledge that may not be available to you.

SPEAKER: Thank you so much.

DR. COOK: Okay. Hi. My name is Dr. Jonathan Cook. I'm a skin cancer surgeon at the Duke University Medical Center in Durham, North Carolina. It's a privilege to be here today.

I had a history of childhood eczema or atopic dermatitis that kind of became quiescent as I became an adolescent. And then when I started my career in healthcare, I developed a extremely debilitating hand dermatitis. My hands were affected with an itching, burning eruption that limited my work and, quite frankly, gave me grave concerns that my career would be limited.

The symptoms really started late in my

training, but they really started to become crippling several years after I began clinical practice. I've been in practice for 28 years and the symptoms became dramatic enough that not only did I have fears that my occupational success would be curtailed, but I was to the point that I required treatment with systemic corticosteroid medications multiple times a year just to be able to do my job.

I finally saw an occupational dermatologist, a contact dermatitis specialist, about 15 years ago under the presumptive diagnosis of a glove dermatitis, which can be quite problematic in healthcare providers. I had already transitioned out of latex-containing products like many healthcare providers were doing at that time, but my symptoms persisted, so I sought professional help. I underwent extensive patch testing under the direction of a suitable specialist, again with a presumptive diagnosis of contact allergy of a glove, which, again, is quite common in healthcare providers.

After an extensive series of patch testing, I had a relevant positive reaction to a chemical called 1,3-diphenylguanidine, which is in latex gloves as an (inaudible) in those gloves. But oddly enough, the chemical is also present in in some non-latex-containing gloves, even the isoprene gloves that my health system had recommended that we transition to.

So after I identified, with the aid of my specialists, this potentially offending chemical, I sought out the use of a product that did not contain 1,3-diphenylguanidine and, in fact, there is one brand of non-latex surgical sterile gloves that do not contain this offending chemical. The gloves are not easy to get, but the identification of the cause of my allergy and the avoidance of this allergen has dramatically improved my quality of life. My hand dermatitis has resolved, my ability to continue my surgical practice has been preserved, and my comfort with my occupational requirements is restored.

The value of patch testing in my case

was that it identified a single putative agent that may be related to my dermatitis. Once that antigen or that chemical was identified, a strict avoidance of that has resolved my hand dermatitis, allowed me to continue to be healthy and productive. Without patch testing, I'm not sure I would have ever identified the cause of my dermatitis because, again, this chemical is present even in many non-latex containing gloves, certainly present in the gloves that were recommended to physicians in my health system. So patch testing has really improved the quality of my life and has improved my health and my care of patients.

So I strongly support the value of patch testing and I would be happy to address any questions further. Thank you.

DR. KASLOW: So FDA would like to thank all the patients for their video testimonials.

And we are now going to go to about a 30-minute panel Q&A session. And for that session we'll be joined by Dr. Aquino, who is the

professor of pediatrics at the Warren Alpert Medical School at Brown University, and is a staff physician at Brown University Health in Rhode Island and in the Division of Allergy and Immunology. And then also Dr. Belsito, who is the Leonard C. Harber emeritus professor of dermatology, Columbia University, Irving Medical Center, and clinical professor of dermatology at NYU Langone Medical Center.

So perhaps to get the session going, maybe I'll first turn to Dr. Aquino and then Dr. Belsito for any opening remarks. And I also ask all of the speakers maybe to turn their video on. And after those introductory remarks, we'll go through about the 10 questions we already have in the chat.

So let's see, do we have all of our panelists this on? I don't -- let me see if I can -- how I can figure this out. View like this. There we go. I think we have our speakers on. How about our additional panelists?

Dr. Aquino, are you on?

DR. AQUINO: I am on, but my camera does not seem to be.

SPEAKER: Okay. There you go.

DR. KASLOW: Yeah. I don't know if you have some opening remarks or thoughts or questions you want to start with.

DR. AQUINO: Oh, absolutely. I want to first thank all the speakers for their hard work and organizing these presentations. They were truly wonderful. And I'd like to thank the patients who gave the testimonials. You can see the impact on, you know, daily functioning, work, and even mental health that contact dermatitis (inaudible), you know, it just reminds us why we're here today. So I thank everyone who worked on organizing the presentation today.

I think I'll start with the first speaker, if that's okay, Dr. Ehrlich. So what lessons have we learned from the history of patch testing and what can we -- how can we move forward?

DR. EHRLICH: Absolutely. Thank you.

So what we've learned is that patch testing has been utilized for many years. It is a safe tool for the diagnosis of allergic contact dermatitis. And it's very important that we can continue to use this tool to the fullest of our abilities and have as many haptens as possible to utilize. Because as we know from the other talks, the more haptens we have available, the more likely we are to find the answers that we're searching for.

DR. AQUINO: Excellent. Dr. Belsito, are you on or should I keep going?

DR. BELSITO: No, I'm here. So I would reiterate what Marcella said, all the speakers were incredible and the patients were incredible. I think that we've really got a good understanding of how important patch testing is.

For Dr. Pacheco, did I understand that 18 percent or so of occupational allergic contact dermatitis would be missed even with an extended panel of patch test? Is that correct?

DR. PACHECO: Well, so the paper of which you were an author, I wish to point out,

suggested that there were supplemental allergens of which 5 percent would not have been identified had they not been included. And another, I guess, 12 or 13 percent that reacted to the regular panel but also needed supplemental allergens. So it does suggest that sometimes you have to broaden the patch testing that you're doing if you want to pick up the relevant allergen.

DR. BELSITO: I think that's particularly true with occupational because you'll have workers exposed to allergens that most of the general population is not and they become sensitized to those allergens and so they're not common --

DR. PACHECO: Yeah.

DR. BELSITO: -- but they're important and so certain industries.

DR. PACHECO: I agree, I agree.

DR. AQUINO: Excellent. I'll go next again. So for Dr. Yu, fellow practitioner in children, what are you seeing in terms of allergic contact dermatitis to topical therapies that we

use for atopic dermatitis? I know one of the patients mentions contact allergy to topical corticosteroids.

SPEAKER: Can you see the --

DR. YU: Yes. So topical therapies for AD treatment, definitely a potential culprit that we always consider, especially in those kids who have longstanding eczema. They've been using something and suddenly they feel like putting this on actually makes their rash worse. I think topical steroids is definitely a consideration.

When we think about potential contact allergens and medications, we have to consider the excipients as well. Common things being benzyl alcohol, propylene glycol, any of these potential additives, lanolin for example, can all be added to different types of topical medications. The steroids, the nonsteroids, the topical calcineurin inhibitors, some of the topical JAK inhibitors, all of those potentially can contain some of these contact allergens that we have to screen for in the right clinical scenarios.

DR. BELSITO: And I have a question for Dr. Chen. Is contact dermatitis in certain body areas, for example, the hands, associated with higher costs?

DR. CHEN: Yes. So we know that certain body parts, like the face and hands, for example, are associated with higher morbidity. And there's especially data for hand eczema that it is associated with a high cost, which makes a lot of sense since it's needed for activities of daily living. You also need your hands for occupational tasks.

DR. BELSITO: Thank you.

DR. AQUINO: Excellent. So back -- I'll ask Dr. Chen a question again now, since she's on as well. How directly does patch testing minimize the cost, cost of contact dermatitis?

DR. CHEN: Yeah, I think it's just about offering timely diagnosis. So it's recommended that patch testing be considered anytime someone has dermatitis that's not easily responding to therapy or before starting systemic medications,

like Dr. Yu mentioned, since some of the time, at least some of the time, we know that patients will improve with just allergen avoidance, and it may spare them the need to go on systemic medications for eczema. So I do think that patch testing used effectively and in a timely manner can greatly increase -- or, sorry, greatly decrease the cost of eczema and contact dermatitis in particular.

DR. BELSITO: Question for Dr. Yu. You mentioned that patch testing is safe in children. Have you ever seen a child sensitized to an allergen that you tested or otherwise have a significant adverse event as a result of testing?

DR. YU: That's a great question. And then certainly one of concern, right? Because if we are sensitizing kids, we're definitely doing them a disservice. Of the hundreds of children I have patch tested, I have never seen a case of active sensitization in any of these kids. And I think if you look in the literature, you will find that is probably the universal experience across the board.

I think when it comes to active sensitization, perhaps we can think about something like hair dye allergen, like paraphenylenediamine. I think that is the only one I have ever heard of. People tell me maybe there is a little bit of active sensitization, and for that reason we actually don't include it in the pediatric baseline series at all and I don't believe people do in the international series either.

So I think the likelihood of active sensitization is hot -- is heavily debated. Very, very, very unlikely. And if so, two things that most kids are probably not being exposed to and not being tested to either.

DR. BELSITO: But you may want to aim test PPD in that child with the black henna tattoo reaction.

DR. YU: Yes. Yes, yes. For that rare kid that may be in contact with it or for that kid, for example, whose mother probably dyes her hair and then, you know, sleeps on the mother's

shoulders and then really face is always in her hair, things like that. There has definitely been a suspicion for that, but I think the likelihood is low.

DR. BELSITO: Thank you.

DR. AQUINO: Great. Good morning, Karin. I'd like to say good morning to Dr. Pacheco, my dear friend. The question in the chat that I thought was very interesting. So in terms of occupational contact dermatitis, how or if do we factor in factory site visits or working with national employment agencies to kind of help us identify the allergens and improve the career of our patients?

DR. PACHECO: So if I understand you rightly, it's how do we identify the allergens that may be relevant in the workplace?

DR. AQUINO: Yes. And then is there a role of working with national employment agencies, like the National Safety -- like OSHA to kind of go into the workplace and help us make the workplace safer for the patient?

DR. PACHECO: Well, you know, I have been thinking about this because this, this whole symposium relates to the development of more patch test extracts and the occupational component is really important. I think sometimes what happens is that you see case reports or small case series or even an individual case that suggests an allergen that we haven't really thought of. And I think it's those kind of case reports that drive the search for new allergens.

You know, a lot of the national databases in some ways deal with allergens that are already known. And yet we all know that there are a bunch of them out there that we don't know.

DR. AQUINO: Thank you so much.

DR. BELSITO: Question for Dr. Ehrlich. You were talking about the epidemiology of contact dermatitis. What does this tell us about treatment, disease?

DR. EHRLICH: Yes, thank you. Regarding the epidemiology of allergic contact dermatitis, what we see when we look at the data is that

contact dermatitis has very high prevalence in the U.S. and in Europe as far as when you look at skin diseases as a whole, and the costs associated with allergic contact dermatitis and the morbidity associated with this diagnosis are significant. So it's very important that we have the tools necessary for diagnosis of this condition.

DR. BELSITO: Thank you.

DR. AQUINO: Excellent. A question in the chat and I think this could be addressed to all the speakers here. There was a comment asking for more of the speakers to answer back when the questions are relevant to them. So if patch testing is so important, like we're discussing today, why is it so hard for patients to find someone who can patch test them? And myself and Dr. Pacheco, along with Dr. Fonacier, who will be speaking later today, did publish the state of patch testing in allergy and immunology fellowships.

DR. PACHECO: Well, I'll start because we did that paper together. Nany patients say

it's been difficult to find a dermatologist willing to patch test. And so more and more it's sort of turning to allergists to do the testing. What our work group report basically said is that we need more directed education in the allergy immunology fellowship in terms of how to do patch testing, how to do the interpretation, how do you make the selection of the allergens that are relevant?

So, I mean, it's hard. Patch testing takes time. Right? You need several visits, you need access to the extracts, and you need access to somebody experienced enough to interpret the results.

DR. BELSITO: Thank you. Question for Dr. Chen and actually all the speakers. Does delay in the diagnosis of allergic contact dermatitis result in higher costs just not considering office visits and medications?

DR. CHEN: Thanks for bringing that up. Yes, I think that a delay in diagnosis of allergic contact dermatitis results in increased costs

across the board. So increased lost work days or the costs associated with the decreased quality of life, like I was mentioning, increased restricted activity days. And I think we've all seen patients who have their lives dramatically changed by a timely diagnosis. Would love to hear others' thoughts.

DR. PACHECO: I would add to that that you -- with timely diagnosis, you then reduce the risk of having permanent, say, hand changes or skin changes that can't be reversed. Right? So you have to catch it early enough in order to try and return the skin to its natural state.

DR. BELSITO: Thank you.

DR. AQUINO: Thank you. So again, I think this is a question that can go to everyone, but it was addressed to Dr. Yu, and this was something that was alluded to in the earlier talks this morning, is why sort of we need to do an extended panel. Like why can't we start off with just a basic panel like the TRUE Test that Dr. Ehrlich mentions? Why do we need to go to the

extended panel? Why should we go to the extended panels right away?

DR. YU: Yeah, I think, you know, so I always teach my medical students and residents, you know, when it comes to patch testing, more is almost always more. Part of the reason for that is if you were to ask a patient about their exposures, they are not going to know what they need to tell you that they are being exposed to because seemingly innocuous things that they use in a day to day basis that might be causing the rash, they don't remember to mention because to them it, it was something that was deemed as safe or clean or whatever it may be. So by not doing an extended series, as I've shown kind of in my talk, that you are probably going to be missing the vast majority of potential contact allergens.

Data really shows that the TRUE Test, for example, will miss at least 40 percent of relevant contact allergens in children. We show that the TRUE Test can only pick up about 50 percent of the top 10 allergens. Whereas some of

the other tests where maybe we are able to test more comprehensively and we are a little bit more nimble about putting in relevant allergens to today or emerging allergens, for example, we are able to detect far more relevant allergens. And if we're asking the patient to go through the patch testing process, we rather do it as comprehensively as possible so we can get them to an answer. Because I think sometimes people can also be falsely led to believe that if you are testing negative on a limited patch test series, the conclusion might be, I don't have an allergy to anything, which is actually not true. Because if you're missing 40 percent of it, well, you know, you very likely could be allergic to something. We're just not finding it.

So I do think that if we're going to do patch testing, we should do it right as a service for the patients. We should do it in a way that most likely will detect their contact allergen given their exposures. And I'm afraid that if we do test only to a very limited series, we are

actually doing a disservice to some of these folks.

DR. BELSITO: I mean, I would just add, Jeff, that, you know, number one, patients don't have a difficulty identifying the allergen because the responses are delayed in time and they could be using this product for months and not have an issue. The other thing is, you know, as opposed to prick testing, which is an immediate read, our patients are going without bathing for anywhere from five to seven days. Their back is covered, there's lost work, for kids there's lost activities at school. So that's a -- patch testing is a big impact on an individual's life. So you only want to do it once and not say, oh, well, I forgot to do this, maybe you should come back for another week.

DR. YU: Right. And I think to kind of, you know, circle back a little bit on the access issue that we are also seeing in the United States and probably around the world when it comes to patch testing, you know, you're absolutely

correct. I do think there is a lack of people doing patch testing outside of major city centers. Right? I mean, in some major city centers, you have two, three patch testers at best in some of these biggest cities and in small, smaller cities or, you know, more rural areas, there are zero past testers, period.

But I do -- but I am a little bit afraid that some of this may be due to the restrictiveness of getting patch test allergens and really getting started. Because a lot of our graduating dermatology residents, allergy fellows, don't really know where to get started when it comes to how are we going to set up this patch testing clinic? Where do I get these allergens from? You know, and all of that. And I think some of those restrictions is really preventing some of us who may be, you know, wholeheartedly really wanting to do something like this and try to help the patient and be very limited.

I do think at the end of the day, dermatologists probably are the leading experts

when it comes to patch testing because we are -- you know, one of the most important things I think for patch testing is having that pretest probability of is this an allergic rash or not? And I think as dermatologists are able to tell you, this is an allergic contact dermatitis, this is rosacea, this is lupus, because a lot of those things can look very similar. And just because it's red and itchy doesn't mean it's always something that we can patch test.

So I think as dermatologists, we are acutely aware of being able to differentiate between some of those conditions, really pick the right patient for patch testing, and then patch test them comprehensively. Because if all we have at our disposal is a very limited series, we're really not going to be able to help as many patients as we all hope that we could be. And as you have already heard today, this is a very safe environment and very, you know, sensitive, and pretty decent positive predictive value in the right patients type of test. And I do hope that

we are able to kind of expand our ability to patch test going forward.

DR. KASLOW: If I might just have a quick follow-up on that one. Can you take me off mute, please?

SPEAKER: Oh, I thought you are. No, you are. Can you hear Dr. Kaslow?

DR. YU: Yes. Yes.

DR. KASLOW: Okay, great. So I actually to want. I wanted Dr. Chen maybe to take -- make a comment about how much patch testing is really a health equity and access issue, both economically and socially.

DR. CHEN: So I think, unfortunately, access is an issue for all parts of medical care. We know that patients from lower socioeconomic backgrounds have less access. There's less patch testing. That's been shown in database studies, claims database studies. And I think that that is an area where we are actively working on it. I know the American Contact Dermatitis Society, we have put significant effort out into kind of

educating more folks so that they feel empowered to patch test. We also have a number of initiatives within dermatology, kind of increasing virtual visits and leveraging those to improve our access. So I think it's a real problem currently and we're aware of it and trying to address it.

DR. KASLOW: And maybe just a really quick follow-up on in terms of testing people with darker skin.

DR. CHEN: Yes, we do feel that darker skin types have different presentations on patch testing. And this is something that actually in collaboration with the American Academy of Dermatology, we recently had a course, the American Contact Dermatitis Society recently produced a course for dermatologists on the topic of interpreting patch tests in skin of color. Because it does look different, it's more hyperpigmented, it's less obvious, and there are other nuances, like it might be more papular and so forth. So we are aware that that is an acknowledged gap in the population and it has been

gaining increasing attention lately in dermatology. So we do have quite a bit that is in action trying to address that gap.

DR. BELSITO: Question for Dr. Yu, but really I think for all the panel, and this was really brought up by the patient of Dr. Susan Nedorost, specifically the question was, do pediatric patients need repeated patch testing over the years as they grow? But I would say, do even adult patients need repeated patch testing sometime?

DR. YU: Yeah, and I think that is, you know, that that is a great question because we are not sure if kids "grow out" of their allergens. Right? There are some studies that show certain allergens, like aluminum, for example, the prevalence of aluminum allergy is much higher in kids between the ages of zero and five, then really decreases throughout, you know, childhood and then adolescence, too. Does that happen for other allergens as we get further and further away from exposure? Because our exposure to aluminum

in children largely is coming from certain types of vaccines and things like that.

So I don't think we know the answer to whether or not people routinely kind of grow out of certain allergens. But I do think repeat patch testing, like that patient, is important when patch testing maybe to a certain series of allergens. It gets you part of the way better, or you're completely better, and then you start developing the rashes again. Because can you be sensitized throughout life? I think we all know the answer to that. The answer is absolutely yes. Right? You can get a new sensitization when you're 90 years old or you can get a new sensitization when you're 15 years old. Age is really not a discriminating factor here.

So I do think repeat patch testing, especially when the clinical scenario presents itself, that looks like ACD, absolutely, if avoidance of the original allergens has not helped.

DR. BELSITO: Thank you.

DR. PACHECO: And I wanted to add a comment on Dr. Belsito's note in the chat saying that patients don't understand actually that you have to be exposed to develop an allergy. And again, often these are products that they may be using all the time. So how could that cause a problem?

DR. BELSITO: Yeah, I think the latency is really hard. You know, as opposed to IgE, you have a shrimp and you break out in hives, you can sort of see that correlation. It's not true with patch test allergens.

DR. AQUINO: Question for Dr. Ehrlich. So supposing we have a patient with atopic dermatologists and we may not have a lot of backspace to patch test, what are other locations that can be used for patch testing?

DR. EHRLICH: So the inner arms, sometimes the thighs, even the abdomen worst-case scenario. That's not the best area because people bend over. But yeah, definitely thighs, inner arms, because those areas you're not flexing a

joint over, so you can usually get the patches to stay on those areas.

DR. BELSITO: And for Dr. Yu, what is -- in your experience, what percentage of patients with atopic dermatitis have concomitant ACD?

DR. YU: I might have a little bit of a bias here just because, you know, most of the kids that I end up getting referred for patch testing have atopic dermatitis. So I would say think, you know, probably for me at least, closer to 50 percent of those kids have some sort of ACD that is superimposed on their atopic dermatitis.

If you look at the general literature, they will oftentimes quote numbers around 20 to percent of kids who have atopic dermatitis have allergic contact dermatitis. Do I think every kid with AD should be patch tested for ACD? I definitely don't. I do think most of those kids probably have bona fide atopic dermatitis on its own. But I do think that there is a significant subset that we're probably missing of kids with AD that have some superimposed ACD. And the only way

we're going to find that out is by patch testing them.

DR. AQUINO: All right. I think one final question came up in the chat. This is from Dr. Fonacier, my old mentor and colleague, and she's asking, and I think anyone can answer this question, can someone talk about the reproducibility of patch testing?

DR. YU: I think this really comes down to your ability to interpret patch testing. Right? I think sometimes if you are not an experienced patch tester, you may misinterpret an irritant reaction. You may misinterpret a doubtful reaction for a positive reaction. And in those cases, if you were to repeat that, you are not likely going to find a positive reaction again on another patch testing.

But that being said, for a lot of my patients who are coming to me for second opinion after having been patch tested by someone who may be less experienced with patch testing, I oftentimes find not only, you know -- so, yes,

sometimes I do find reproduced allergens, certainly for the most common ones, like nickel, for example, which is so easy to see and very often quite positive in some of these patients. But I do pick up on some of the allergens that perhaps people misinterpreted as being an irritant or misinterpreted as being a doubtful reaction, or, more importantly, patch tested them to a much more expanded series where now I am finding new allergens that are not only positive, but are clinically relevant that they would have never known about if we didn't go about the more expanded routes.

DR. BELSITO: But it is a bioassay, and so things that patients are doing can interfere with it, too, like sun exposure, inadvertent steroid use. So there are things that can, you know, interfere with the testing. And you need to question the patient before you start testing them as to whether they may be on any of those agents that could interfere with your reactions.

DR. YU: But I do think, Don, if you

were to patch test someone, I were to patch test after, I bet we would find very, very, very similar reactions between the two of us. So I do think that between experienced hands, reproducibility is quite high and quite good.

DR. BELSITO: I would agree. And question for you, Jeff, that next to the last patient was talking about newly diagnosed propylene glycol allergy. With propylene glycol and steroids and, you know, some of the newer medications that have come out for atopic dermatitis, what do you find the incidence of propylene glycol allergy is in kids?

DR. YU: Gosh. I think the likelihood of propylene allergy, if you were to look at all of the kids in general, not very high. And I don't think that is different from the adult population either. I would probably estimate 2 to 3 percent, you know, overall probably have some sort of propylene glycol allergy.

That being said, when it is positive, it is highly relevant because which kid with atopic

dermatitis has not been exposed to a topical steroid that likely has propylene glycol in it. Right? And a lot of our nonsteroidals nowadays also contain propylene glycol. So it does become a challenge to make sure that we can find a appropriate alternative for them that does not include the excipient.

We've also seen propylene glycol in some oral medications. So liquid antihistamines that are given to children can also have propylene glycol. And I've certainly seen cases of kids who have a full body atopic dermatitis that was thought to be just very severe atopic dermatitis, in fact, be a systemic allergic contact dermatitis to ingestive propylene glycol.

So I think that it is common enough and I think it is severe enough that we should patch test kids to propylene glycol routinely. But do I see it in every kid? I don't, which is, you know -- which I think mimics blends of propylene glycol overall in other studies that have been published.

DR. BELSITO: Thank you. Marcella, are

you seeing any questions that I've missed?

DR. AQUINO: No, I was just taking a quick peek. I don't see any other questions that we've missed and I do think we're probably running out of time, if I'm not correct.

DR. KASLOW: Correct.

DR. AQUINO: So then on behalf of myself and Dr. Belsito, we'd like to thank again all the panelists for the robust discussion and the patient testimonials and the participants for today's morning meeting.

DR. KASLOW: So let me also thank the two panel moderators and let me thank all of our panel presenters for really doing a nice job setting the stage of this workshop and really validating the unmet need and the burden, be it economic, social, or mental health.

So we're going to now to take a break until 11:20 a.m. Eastern Daylight Time and then we'll turn the moderation over to Dr. Sharon Tennant for the session on Regulation of ACD Diagnostics. So thanks again all.

DR. BELSITO: Thank you.

DR. AQUINO: Thank you.

(Recess)

DR. TENNANT: Good afternoon, everybody. Can you -- I assume you can hear me okay.

SPEAKER: Yes, we can.

DR. TENNANT: Great. Thank you. Welcome to the second session of the ACD Workshop. And this session will be on the "Regulation of Allergic Contact Dermatitis Diagnostics." My name is Sharon Tennant and I'm the acting director of the Division of Bacterial, Parasitic, and Allergenic Products in the Office of Vaccines Research and Review.

We have four speakers in this session. We don't have a scheduled Q&A for this session, but if time permits, we will take some questions before our lunch. But we'll plow through each of the presentations first and see how we do with time.

It's my pleasure to introduce the first speaker of this session, Dr. Ronald Rabin. He is

the chief of the laboratory of immunobiochemistry and he really has been instrumental in spearheading this workshop and bringing everybody together.

And with that, I will hand over to Ron.

DR. RABIN: Okay. Thank you, Sharon. So this is going to be a short talk because the history is of regulation of these products is fairly straightforward. I have no conflicts of interest. And now there we go.

And so the first thing to know is, of course, that there's a law behind how we regulate these. And Dr. Kaslow referred to that, that they -- that we have the authority to regulate these patches by Section 351 of the Public Health Service Act, which defines a biological product as a virus, therapeutic, serum, toxin, antitoxin, vaccine, blood, blood component or derivative allergenic product applicable to the prevention, treatment, or cure of disease. And then there's a definition of a drug. And then this was clarified in a Federal Register Notice in 1986, that

chemicals that are intended for commercial marketing and used for patch testing in humans are biological products and, therefore, they're licensed under the U.S. Public Health Service Act, including labeling indicating use for diagnosing hypersensitivity.

The first patches that actually went through the approval process and were approved were these 11 patches. Pharmacia was the company that had them. They were 12 patches, 11 haptens and the negative control. And I think you've seen these chemicals enough this morning, I won't read them off to you.

The next sort of advance, if you will, was the TRUE Test 23 hapten panel that was approved in 1994. And then let's see. Hold on. I'm sort of-- sorry, the advanced setting. Okay, there we are. I see now.

Okay. And then in 2007 [sic] and 2008 we approved five additional haptens and seven additional allergens in 2012. And that sort of -- and then what happened was that SmartPractice then

designed a rubber panel and that was approved in 2017. These five allergens and then -- and obviously the negative control are all part of the standard 36 patch TRUE Test panel. But here they were marked -- they're in this platform of the rubber panel.

So how do we -- the clinical studies that we've been having -- that we've been asking for are what we thought -- we have considered to be a fairly low bar, to be quite candid. They're open label, they're not randomized, they're not blinded. They include a number of subjects that are known to be sensitive to the hapten. And then we've included -- we've said that we would want to include consecutive subjects with a history of contact dermatitis without previous past test reaction. And I want to go back to that in a second. But then that would be compared with a petrolatum or solvent-based positive control in a Finn Chamber type setting as gold standard. And the reported results are simply agreement between the two tests and what would be considered

sensitivity and specificity.

Now, it's interesting that we did choose the consecutive subjects with the history of contact derm without previous test reaction because I sort of wonder whether or not that was the best way to go about it. And I'm looking forward to hearing some of the discussion whether or not a better way to have gone about it would have been consecutive subjects who would -- might have gone to a dermatologist office with no suspicion of allergic contact dermatitis. And then, you know, presumably, you could get a very solid number about, you know, irritants and questionable reactions and get a little bit more information about performance of the patch.

But that being the case -- and then when we ended up publishing, when we ended up, you know, granting licensure for these patches, we were -- you know, we scratched our head a little bit because some of these numbers that came up were less than ideal. And so basically, what we did was we just simply published the data, you

know, as they were, so that the practitioner could understand the quality and the performance of the product, you know, as it tested.

And this is one of them, you know, the MDBGN. And you could see that the sensitivity was, you know -- and was not, shall we say, ideal for this particular patch either in the group that was thought to be patch test positive and those, excuse me, please, and then those who were the consecutive subjects. And I sort of wonder whether or not part of the problem with that is that if somebody knows that they're sensitive to the particular chemical and then you don't see them for, you know, who knows, 10 years, you know, they might not have that reaction, that amnestic response might not occur with the very first exposure right after that. It might take a little bit longer. But at any rate, that's -- those are the numbers we see.

This is one, the hydrocortisone 17-butyrate, that certainly gave some better numbers and that was sort of the range of the kind

of numbers that we were dealing with. And quite frankly, from our perception, a little bit of the frustration with regard to whether -- what kind of bar do we set for these products and what kind of data do we need to really be comfortable that we're licensing the best patch to as a diagnostic device for these products?

But that being the case, here's the TRUE Test panels. We're going to hear more about these. Obviously, these are the panels that are available in the U.S., so I won't burden you with them. That's where we are now, along with these, which, of course, include these five allergens that are in the rubber panel. And that's kind of where we are.

And that's all that I'm going to share with you, that I have to share with you about where we are with licensing these in the U.S. If I had more to say, you probably wouldn't need this workshop.

DR. TENNANT: Great. Thank you, Ron. We'll move on now to our next speaker, Dr. Joel

DeKoven. If you can share your slides, please, Dr. DeKoven.

DR. DeKOVEN: Actually there was a technical problem, so it's going to be done on your end. There we are. So whenever I say "click," then you can move forward with the slide.

SPEAKER: Thank you.

DR. DeKOVEN: I'm going to be talking --

DR. TENNANT: Go ahead.

DR. DeKOVEN: -- oh, sorry.

DR. TENNANT: I'm just going to briefly introduce you. So, Dr. DeKoven is a professor in the Department of Medicine at the University of Toronto, Canada. He's currently a consultant in the Division of Dermatology at Sunnybrook Health Sciences Center and the Division of Occupational Medicine at St. Michael's Hospital. He's a diplomat of the American Board of Dermatology and has Royal College specialty certifications in both dermatology and public health and preventive medicine, as well as a master of Health Sciences from the University of Toronto. And he's going to

be talking about the "Regulation of ACD Diagnostics in Canada."

Please, over to you, Dr. DeKoven.

DR. DeKOVEN: Thank you. Thank you to Ron for inviting all of us to present these Important topics. Click.

This is an outline of what I'm going to be talking about. And we've had some discussion about what is patch testing. I'll go through a drug and food regulation Canada with respect to topical allergens and the regulatory oversight of the topical allergens, how they're licensed in Canada through the regulatory pathways, and what are the benefits to the population and physicians as a whole. Click. Click.

That's good. Okay. We've already found out that patch testing, in a manner of speaking, is a gold standard diagnostic tool for type 4 hypersensitivity. And we've seen that it is safe in both the adult and pediatric populations. Dr. Jeff Yu provided a great talk about that. And there's a body of literature that supports that

and along with the long history that was presented by Dr. Ehrlich. They're considered to be safe and there's a few known minor complications.

What allergens are going to be selected depends on the patient history that's extracted, the physical examination, and also the availability of allergens. And I guess I could say in Canada, availability of allergens is not really at the top of the list of problems with respect to patch testing. Interpretation, of course, requires a lot of training and experience, and this enables avoidance of particular personal allergens and then suitable substitutions, as we heard with one of the videos of appropriate accelerator-free gloves. Click.

It's a personalized diagnostic procedure, so we're using it as a bioassay. And most of these allergens that are being tested have been available globally in various approved forms for many, many years. Of course, no two patients have the exact history or the potential contact allergen exposure. And comprehensive topical

allergen availability is really essential to me and my practice and my colleagues in order to identify the relevant allergens. And this will facilitate avoidance. Click.

So some of what I'm going to talk about is for the benefit of FDA regulators and some is for the general audience. And Canada has a multilayered system for regulating drugs and foods. And before they're authorized for sale in Canada, Health Canada will review for safety, efficacy, and quality. The substances will be divided into drugs, device, or some combination. And once it's classified as a drug and not a device, they're further categorized by natural health products, biologics, or pharmaceuticals. The classification determines the regulatory pathway, whether it's a drug, device, natural health product, and the Biologic and Radiopharmaceutical Drugs Directorate is responsible for regulating these biologics. Click.

This is just the schemata of showing how

drugs and foods are regulated in Canada and we can see divided up under the Food and Drugs Act in Canada: Drugs, food, devices, and cosmetics. So depending on where we are under the drug category will determine what regulations apply. Click.

Here we're talking -- no, they went too fast here. We're talking about the biologic division and what regulations apply to that. So everything I'm going to be talking about derives from the biologic division. Click.

So in order to sell topical allergens it needs Health Canada authorization and there's a screening submission for regulatory compliance and the BRDD provides the final market authorization of the biologic drugs. There's another division that ensures compliance with plain language labeling. And these allergenic products fall under Schedule D of the Food and Drugs Act and they're subject to following divisions of Part C of the Food and Drug Regulations. So we have a general requirement applicable to all drugs and we have establishment, licensing, good manufacturing

practices, and other regulatory requirements. Click.

And an onsite evaluation of manufacturing facilities as well as in-house laboratory testing may be conducted as part of the regulatory review. So it doesn't have to be conducted in Canada and this may be through agreements with other jurisdictions, for example, countries in the EU. Click.

So there's topical allergens that are submitted under a DIN-B submission package and this has various regional informations, but it also has a summary of the quality, chemistry, manufacturing controls, nonclinical study, reports and clinical study reports. Click.

Aside from that, there's two main divisions. That's the drug establishment license and the good manufacturing process practices. Click.

So the drug establishment license is necessary in order to distribute these topical allergens in Canada and good manufacturing

practices need to be demonstrated. Click.

Under that, Health Canada can enforce regular inspections of facilities looking at manufacturing, packaging, labeling, testing, et cetera. And there's agreements between Canada and many EU countries so that inspections that are done by countries, let's say Sweden, for example, or other countries in Europe, there are agreements with Health Canada and those countries. Click.

So there is the agreement called CETA, which recognizes mutually compliance and enforcement program of GMP for the pharmaceutical products between the European Union and Canada. And this has been in effect since 2017. Click.

And these list of products within the CETA protocol will include human pharmaceuticals, human biologicals, and immunologicals such as topical allergens, and human radiopharmaceuticals. Click.

This provides a link to the countries that have agreements with Canada and there's many of them. To give you an example, we have Austria,

Belgium, Denmark, Finland, Germany, Ireland, Italy, Portugal, Spain, et cetera. Next.

In 2017, this was the groundbreaking measure for approval of topical allergens. Health Canada issued four DIN numbers to -- DINs to distinguish subgroups based on the type of active substance and associated vehicle. Click.

So subgroup 1 consisted of 24 products that were registered. An example would be formaldehyde 2 percent in water. Click.

Subgroup 2 were solid active substances in a liquid vehicle of all 29 products. An example would be cadmium chloride or shellac. Click.

Subgroup 3 would be liquid active substances in a semi-solid vehicle, like petrolatum; 162 products were approved in this category. And examples would be hydroxyethyl methacrylate 2 percent in petrolatum or bisphenol A epoxy resin 1 percent in petrolatum. Click.

And subgroup 4, a solid active substance in a semi-solid vehicle. And this was the bulk of

the approval, 343 products. An example here would be potassium dichromate 0.5 percent in petrolatum or, for example, lidocaine 5 percent in petrolatum. Click.

So by the end of 2024, there were 475 topical allergens on the Canadian market. Now if you add up all of these here, you're going to have 558. And so some of the remainder were not distributed either for commercial reasons or supply chain issues. So again, at the end of 2024, we had 475 topical allergens on the Canadian market in contradistinction to what's approved in the United States. Click.

A drug identification number is required and it's issued by Health Canada when it's felt that the product benefits outweigh the risks. And this is based again experientially on third-party studies, research articles, peer-reviewed papers, journals, real-world data, and the types of presentations that you've seen from some of my colleagues. All of these drugs are categorized under Division 1 under the Food and Drug Act.

Click.

Now, for a new drug submission a notice of compliance is issued by Health Canada. But this may require actual clinical and nonclinical studies to demonstrate the safety and efficacy of a new molecule or a new potential drug. And these drugs are categorized under Division 8. So the approval that you saw of those four different categories of topical allergens are all under Division 1 based on literature review, et cetera. Click.

So for those that are not Included under the 558 topical allergens that have been approved as of 2017, the process is still under discussion. Now, if the product has a unique ingredient or a new indication that's atypical for allergen extracts, then a new drug status regulatory framework would apply and that would be under Division 8. Click.

So once again, in 2017, there was a globally distributed portfolio of 558 approved topical allergens registered with Health Canada.

All Canadian patch testing physicians have access to all of these topical allergens to test their individual patients. And this includes both personal and occupationally related topical allergens and includes both adults and pediatric. And this clearly allows for a more precise individualized diagnosis, as we've heard earlier today, enhanced quality of life.

Now, there are some anticipated minor adverse reactions reported by physicians where these are well managed. And it also allows for research groups to have access to the full range of topical products. So that would be like the International Contact Dermatitis Research Group that I'm a member of and the North American Contact Dermatitis Group, which I'm also a member of, and that supports our ongoing research initiative. Click.

So, as I mentioned earlier, these topical allergens are under Division 1. Again, going on historical precedent, they're not considered new drugs as other things would be

under Division 8. And these topical allergens are widely used and individuals may already be significantly exposed just through everyday contact, through personal care products, cosmetics, occupationally. And all of the existing 558 went through the DIN-B pathway. Click.

So what are the benefits to physicians and to patients? Well, clearly the availability of all of these allergens allows us to identify putative allergens in our patients so that they can avoid contact in the future and also facilitate substitution. And this, obviously, increases quality of life for our patients. And the Health Canada relies on their own evaluation and also agreements with other countries such as those that I mentioned in the EU. Click.

So, you know, we know that there are many confirmed sensitizers on the market, you know, over 4,000, and we can't test all of them, but we do have access to over 500. And by having a wider range of allergens, we have less

underdiagnosis or misdiagnosis of patients. And we also enhance quality of life and cut down some of the costs that Dr. Chen was talking about in terms of occupational costs and unnecessary indirect costs. It also allows for expansion of research in Canada. Click.

So in summary, in Canada, since 2017, we've had eight years of demonstrating stability and consistent access to these products. It's a streamlined approval process, especially for all of the allergens that have been available for years. Mentioned almost 500 are approved in Canada now and on the market. And this allows for a lot of flexibility. Next.

So to close, the DIN-B registration is what facilitates ACD diagnostics in Canada. And this is approved for extracts that have been sold in Canada for, in quotations, "sufficient time," so for many years. And again, it acknowledges the longstanding clinical safety of these topical allergens.

And I will mention that Canada is quite

vigilant with respect to allergens. So there's something called the Cosmetic Ingredient Hotlist. And on that hotlist such allergens are regulated such as methylisothiazolinone and methylchloroisothiazolinone/methylisothiazolinone MCI/MI. So in Canada these are banned in personal care products that are meant to be left on the skin and they're approved from 15 parts per million and lower in wash-off products. This is quite different than the United States, where there is no regulation in that regard for personal care products. So as a result, certain products in the United States, like sunscreen and moisturizers, et cetera, can still have those well known allergens pointed out earlier as being the second most common allergen in the world at one point. So we have, also, possible increased labeling of many fragrances for personal care products coming in the near future, similar to the labeling that's required in the EU.

So my closing point is that we have definite regulation in Canada, but when it comes

to topical allergens that have a long history of usage and safety I believe that we have a very flexible, pragmatic approach to approval of ACD diagnostics in Canada.

That's that. Thank you.

DR. TENNANT: Thank you very much, Dr. DeKoven. Next we will move to Europe. Dr. Vera Mahler from the Paul Ehrlich Institute in Langen, Germany, will present. She's the head of allergology at the Paul Ehrlich Institute. She's a board-certified dermatologist, allergist, and occupational dermatologist. She's been a practicing dermatologist and allergist scientist and lecturer at the Department of Dermatology for 24 years and has served as a speaker of the Interdisciplinary Allergy Center at the University Hospital, Langen, Germany. She is currently an associate professor at the Medical Faculty of the Friedrich Alexander University Erlangen-Nuremberg in Germany. It's a mouthful. And she's going to be talking about the "Regulation of ACD Diagnostics in the European Union."

Dr. Mahler, are you able to share your screen?

DR. MAHLER: I think so. So do you see my screen?

DR. TENNANT: It's coming. It is -- are you able to switch it to --

SPEAKER: There we go.

DR. TENNANT: Perfect. Thank you.

DR. MAHLER: Yeah. So thank you very much for the kind introduction and the invitation to report on "Regulation of Allergic Contact Dermatitis Diagnostics in the European Union." The presentation represents my personal views, not necessarily an official opinion of the Paul Ehrlich Institute. I do not have a conflict of interest.

So the regulatory status of allergen products in the European Union is based on Directive 2183, which is the Directive for Medicinal Products for Human Use. And in Article 1 the definition is given for test and therapy allergens and all our medicinal products. And a

medicinal product in the European Union can only be placed on the market if a marketing authorization has been granted by a competent authority.

So test allergens comprise in vivo diagnostics for type 1 and for type 4 allergy. And just to give you a number, what we have as authorized allergen products in Germany, we have 60 AIT products for immunotherapy, we have almost 400 test allergens for the diagnosis of type 1 allergies, and 167 epicutaneous patch test preparations for the diagnosis of allergic contact dermatitis. And all the products can be found on the homepage of the Paul Ehrlich Institute following this link.

So we heard already there's differences between type 1 allergy and type 4 allergy, and so there is also differences in the regulation of type 1 test allergens and type 4 test allergens. And these differences are based on the different pattern mechanism of the allergic reactions, the different medicinal use, and also the risks linked

to these products. The differences to accommodate for these special characteristics of the products, differences exist for the regulatory requirements and especially concerning the extent of data which need to be submitted for a marketing authorization application.

And indeed there is three different types of marketing authorizations in Europe. There is the full marketing authorization which requires a full data set, including product-specific data from clinical studies carried out by the applicant. So this is normally what is needed for a AIT product. Then there is the mixed marketing authorization where bibliographic data, together with a very limited set of own data, clinical and nonclinical, carried out by the applicant have to be provided. And then last but not least, there is the well established use, and that is actually the type of marketing authorization application which applies most regularly for patch test products in the European Union and in Germany. Here, results of a

preclinical test or clinical trials do not need to be provided by the applicant if the active substance of the medicinal product has been in well-established medicinal use within the European Union for at least 10 years. And here efficacy and acceptable safety must be evident from the scientific literature.

So this is the most typical marketing authorization approach for patch test allergens in the European Union. And these types of marketing authorization can be submitted on a national level or on a European level in a decentralized procedure and then the marketing authorization is valid in different European member states at once.

So these differences between type 1 and type 4 test allergens have been laid down in detail concerning the regulatory requirements in two different guidelines. The one guideline is the CMDh EMA guideline or recommendations on common regulatory approaches for allergen products which was published in 2022 -- or 2020. And the second one is the EMA guideline on allergen

products development for immunotherapy and allergy diagnosis in moderate- to low-size study populations. This is the new kid on the block which was just recently published in June 2025. And both guidelines distinguish meticulously between type 1 and type 4 test allergens and therapy allergens, frequent allergens and rare allergens. And I brought you the table of contents and marked in green which paragraphs are applicable for patch test preparations concerning quality, concerning non-clinical data, concerning the selection for patients, and also the study design for type 4 allergy studies.

So normally for marketing authorization and standard regulatory requirements for in vivo diagnostics comprise quite a number of requirements. For example, for quality validation of manufacturing process for each product, GMP requirements need to be fulfilled throughout the manufacturing process. Details on manufacturing of active substances need to be presented in the product dossier and a full set of stability data

in accordance with ICH requirements need to be submitted for a marketing authorization application. However, type 4 allergens and type 4 patch test allergens have a characteristic and peculiar nature and, therefore, the requirements have been adapted in the European Union for patch test preparations.

So there is the option of a matrix approach for process validation in case of identical product process, production process, a waiver of GMP requirements for the active substance production at the supplier level. So here the GMP requirements start at the front door of the patch test manufacturer. Absence of information of active substance manufacturing is acceptable. Normally, it's typical active substances which are intended for an entirely different use. We have heard of the rubber accelerators, this is a good example, so nobody will produce these under GMP conditions and these would also not reflect the real exposure. And commitments for stability studies may be

acceptable when long-term stability data for at least one batch are available. And this continues for nonclinical and clinical adaptions.

So normally, there is -- animal studies are not necessary for patch test products. Normally, there is existing data and technical data sheets for the chemicals which can be used if compiled concerning clinic. Normally, there is already quite a body of literature which can support the selection of appropriate concentration. And even phase 3 confirmatory studies are not in all cases necessary because there might be registries with well documented cases.

Last but not least, the determination of sensitivity and specificity, which is normally requested for diagnostics, is really hard to obtain for patch test substances because there is not an external standard of truth, not a gold standard as a comparator. And therefore, and this is what the new guideline points out, there is the option to use alternative parameters, like the

reaction index and the positivity ratio.

So for those of you who are not familiar with the reaction index and the positivity ratio, this is longstanding performance indicators for patch test preparations. They can be retrieved and calculated from large patch test cohorts, from patch test networks, and the ideal patch test substance, of course, would only produce allergic reaction reactions, no questionable and no irritant reactions. In this case the calculation of the reaction endings would be equal to 1. If there is as many allergic reactions as there are irritant or questionable reactions, the reaction index will end up being equal to 0. And if there is not a single allergic reaction and only irritant and questionable reaction, this is, of course, what we don't want to have as a patch test substance, the reaction index would be minus 1. And so in reality, all patch test substances somewhere are between reaction index 1, which is the ideal substance, and minus 1 which would be not a good patch test substance.

Positivity ratio gives the percentage of 1-plus reactions among the total of all positive reactions. And we all know that amongst the 1-plus positive reactions not all are always allergic, but there are also some irritant reactions. And so if all patch test reactions would be 1-plus, that would be 100 percent, which would also be alarming. So here I have brought you some real-world data from three patch test substances. And a patch test substance with the positive reaction index and the positivity ratio below 75 percent is a good patch test substance. A negative reaction index and a PR above 80 percent is a problematic patch test reaction with the potential of a high number of irritant reactions.

However, so this is this is helpful for the regulatory assessment. However, even with a problematic situation, that would not automatically lead to rejection of a marketing authorization application, but it would lead to a warning in the summary of product characteristics

to inform the physician that this is a problematic patch test substance and what to expect from it, namely a number of irritant reaction.

So the regulatory approach in the European Union is based on single marketing authorizations for each patch test preparation. The umbrella concept is not in concordance with current EU legislation and is not endorsed by the CMDh Allergen Drafting Group. The CMDh Allergen Drafting Group is a group of regulators from different countries with a high expertise in allergen products which reports to the CMDh, which is the Coordination Group for Mutual Recognition Procedures -- Decentralized Procedures-human. So a standalone dossier for each patch test preparation is necessary. Quality, efficacy, and safety need to be demonstrated for every patch test preparation. And I will show in a minute with some examples why this is feasible and necessary.

So extended parts of the dossier can be identical for similar products, but certain

product-specific requirements need to be fulfilled for each and every product. This is especially the validated determination of active substance content in the finished product and stability data supporting product shelf life of a specific product. So the requirements in the European Union are contrasting to the umbrella approach, which has been recently suggested by one of the patch test manufacturers with reference to Canada.

So we heard already all the 500 products are grouped in 4 product groups: Liquid in liquid, liquid in solid, solid in liquid, and liquid in liquid [sic]. And there is only one marketing authorization for each group. And all the 500 products are summarized in these 4 marketing authorizations with one lead product per group with the full dossier where all the information for one substance are given and all the other products which belong to the group have just a minimal requirement dossier with reference to the respective lead dossier and limited product-specific information.

And what is especially critical in the eyes of the European regulators is that the determination of the active substance content is the done via mass balance calculation. That means it is expected and calculated that in the end product there is in what has been put in the vehicle at the start, but this does not necessarily need to be the case. And also there is a risk based approach for stability analysis, so not every product has stability data. And so this approach has been regarded non-acceptable for the European Union. And I will come back with some examples why.

In the end after marketing authorization process there is a benefit-risk balance assessment. And we heard already the safety risk of patch testing are generally low. So it's just a little bit of substance and just exposed epidermally, so there is not a significant health risk. So this is clear. However, here the risk is significant based on the risk of false diagnosis in case of deficient quality. So

efficacy is only insured with controlled quality and there is quite a number of flaws which may occur if not looked for it: Wrong active substance, suboptimal active substance concentration, inhomogeneity, active substance degradation or evaporation which leads, again, too low concentration, and there might be also contamination with impurities of other haptens. And a wrong diagnosis, false positive, false negative might have a tremendous effect on the consequences which are based on this diagnosis.

So a meaningful diagnosis requires active substance specific product development in data sets and I would like to show few examples. So from our knowledge and experience it is not possible to extrapolate from one active substance to the other, even if they belong to a similar group chemically, for example methyl methacrylate and 2-hydroxyethyl methacrylate, HEMA. The quality issues of the patch test preparations have been published already. And in Germany, therefore, patch test preparations based on data

specific to the products differ in shelf life and manufacturing process. So the HEMA has a shelf life of 24 months, whereas the methyl methacrylate only 12 months. Because a considerable loss of active substance content occurs after 24 months, which the manufacturer himself finds when delivering the requested data.

The manufacturing process is a standard manufacturing process for the HEMA. However, for the methyl methacrylate there is product-specific manufacturing process necessary because even during the manufacturing process there is a loss of active substance. So there need to be at the start a production overage to have the intended concentration at the end. And also a stabilizer has to be added here to guarantee an unobjectable quality of the patch substance.

Another example is propolis. So during the marketing authorization procedure, the marketing authorization applicant proposed two new suppliers and two different batches, country of origin Brazil versus China, and delivered also the

requested analytical data. And here it was obvious, also, especially from the HPLC chromatogram, that the propolis from Brazil is highly different from the initial one and is not comparable at all. That would be a different product. Whereas the product from -- or the batch from China was still similar enough to be acceptable under the same marketing authorization. So the use of propolis harvested in China from the new supplier was approved, whereas the propolis from Brazil was rejected.

In other regions of Europe this propolis product with the Brazilian propolis came on in the market and was tested and showed a high number of positive reactions of unclear clinical relevance. And so this is data from Genova. So the positive frequency of patch testing with the Brazil propolis is significantly higher than the one from China. So it is important to look for the quality of the active substance.

A common concern is how to authorize patch tests substances in Europe containing new

emerging allergens when data for a well-established use is not available. So here the new guidelines give guidance. The way to marketing authorization is highly dependent on the active substance. So -- and most of the time, even if a substance has not been for 10 years in medicinal use, there is some data in the literature, most of the time technical data. There might be a concentration range already from daily products or even from hospital pharmacy-prepared patch test substances where the dossier can be built on. And here the mixed marketing authorization is the way to go. For example for the IBOA (isobornyl acrylate), which is an emerging allergen which is problematic for patients with diabetes using a continuous glucose monitor device, so this is the clue in the device which frequently produces allergic contact dermatitis.

And so the mixed marketing authorization is building on the bibliographic data and requests a small number of own clinical data so the

documented medical need is clear. Non-clinical data, toxicity, and pharmacology can be retrieved from bibliographic sources and also some clinical data already from published cases. And so a small data set is necessary from the applicant. So about 15 patients with the contact allergy and approximately 100 controls will be requested here in this mixed marketing authorization to move forward for a marketing authorization.

So I summarize, epicutaneous patch test products and medicinal products, according to Directive 2183, regulatory requirements for allergen products have been adapted to match the distinct characteristics of the patch test substances. This is all laid down in the two guidelines and especially here in the new guideline published in June 2025. Authorization of patch tests containing emerging haptens is possible via mixed marketing authorization. And the risk of misdiagnosis can be reduced by complying with regulatory product-specific quality requirements. Product-specific quality assurance

is really key to a reliable diagnosis.

I thank you for your attention.

DR. TENNANT: Great. Thank you, Dr. Mahler. Just a reminder to everybody, please post any questions in the chat and hopefully we'll have some time to address those before lunch. So the last speaker for today's session is Dr. Yun Lu, here -- from here at the FDA who'll be presenting on the "Real-World Evidence Program," and giving a perspective from CBER. Dr. Lu is the acting division director for the Division of Analytics and Benefit-Risk Assessment at the Office of Biostatistics and Pharmacovigilance within CBER. Dr. Lu received her Ph.D. in biostatistics from Johns Hopkins Bloomberg School of Public Health and joined the office in 2010. She has extensive experience with real-world evidence reviews and post-marketing safety and effectiveness public health surveillance studies using real-world data.

And looks like Dr. Lu is sharing her screen. We see the -- just the -- yeah, there we go. Excellent.

DR. LU: Yeah. Thank you. Good afternoon. Can someone confirm that you can hear me clearly?

SPEAKER: Yes.

SPEAKER: Yes, I can.

DR. LU: Okay, thank you. Well, good afternoon, everyone. Thank you for having me. Today I'm going to talk about FDA's "Real-World Evidence Program," CBER perspective. So this is my disclaimer. This presentation reflects my view and shouldn't be construed to reflect FDA's views or policies. I have no conflict of interest and also I mention a commercial product should not be construed as actual or implied endorsement.

Real-world evidence and real-world data have been increasingly used to inform regular decision-making. So I want to give you an overview of CBER's RWE program. We have RWE and RWE-related record submissions. For those reviews I will talk about in details later. And after biological products approved, CBER also conduct post-marketing public health surveillance to

monitor an effectiveness of approved product. When CBER detects safety signals, FDA will issue safety communication to communicate with the public and sometimes the safety signal could result in safety changes.

For both safety and effectiveness studies, the results can inform congressional public hearings and also inform advisory committees. For FDA, we have the Blood Committee, Vaccine Committee, as well as the Pediatric Committee. In addition, the work we're doing can also inform CDC's Advisory Committee on Immunization Practices.

The Public Health Surveillance Project could also inform quantitative benefit-risk assessment of products and the lessons learned from public health surveillance can also inform RWE review and motivate discussions with other regulatory agencies. In addition, for our Real-World Evidence Program we have access to millions of individuals in the real-world data and bias actually is more of a concern compared with

the random error. So for CBER we're also conducting method(?) development project to adjust for American funding, which is part of the PDUFA VII hard commitment.

FDA's RWE program actually span all medical product centers. So we have drugs and biologics, CDER and CBER. We also have devices CDRH as well as oncology OCE. So this is a FDA-wide effort. You can see that there are lots of different types of activities for under the RWE program.

Many people have used the term "real-world data," RWD, and "real-world evidence," RWE, interchangeably, but FDA actually has two separate definitions for those two words. Here are the definitions based on the 2018 FDA RWE framework. So the real-world data, there are data. They are routinely collected from a variety of sources and not from a research setting. So you can see there are many types of RWD. And for RWE, this is a clinical evidence derived from analysis of RWD.

So I want to point out that real-world evidence, RWE, is not mutually exclusive to randomized trials. Actually, RWE could be generated by randomized trials, external control trials, or observational studies. RWD sometimes may not be able to generate RWE. So in the next slide I will present a table that was put together by FDA colleagues from multiple centers. They illustrate when can RWD generate RWE?

Here you can see there's a term of interventional study. So that's when a study assigned treatment to a participant. It includes randomized control trial as well as external controlled trials. And the term "non-interventional studies" have been used interchangeably with "observational studies." So when we have non-interventional studies, real-world evidence will be generated and there are different study designs that are typically used. And for interventional studies we will look at randomized controlled trials. If the real-world data is used as a trial endpoint, then

RWE is generated. But if RWD is only used to develop study, for example, identify potential participant, select trial site, then no RWE is generated.

And for external controlled trials, if the external control arm is from RWE source and then RWE is generated. However, if the external control arm using some level data or from another clinical trial, then no RWE are generated. So you can see that many times you will see the term RWD and RWE being shown together, but RWD not always generate RWE.

When we look at RWE submissions there are three key regular considerations. Our first step is look at the data, whether the RWD are fit for use. I will talk more in later slides about fit for use. And then we'll look at the trial or study design to see whether they can provide adequate scientific evidence to answer the regular question. We also look at study conduct to see whether they can meet FDA's regulatory requirements.

FDA has published many RWE-related guidance documents recently. So some of them about data considerations. You can see there are guidance document about registry data, about EHR and claims data. There are also guidance about different study designs, externally controlled trials, non-interventional studies, and RCTs. There are also guidance about submitting RWE, about regular considerations, as well as data standards. In the slides I put in the links for each of the guidance documents.

As I mentioned in the earlier slide, CBER has been conducting public health surveillance to generate RWE. So I want to show you the approach we're using to generate RWE. So we start with asking the right question and then we used fit for use data, which means that we need to have a deep understanding of the data, understand what are the sources of biases in the data, and then we try to minimize the bias by design. We also conduct appropriate statistical analysis to control for bias in the analysis

stage. At the same time, we also plan scientific analysis and also conduct bias analysis to identify and quantify remaining bias.

I want to emphasize on the iterative nature of the approach because lessons learned from our sensitivity analysis and the qualitative biasness can inform our future studies, can help us better understand the data, help us design studies, and plan statistical analysis for future studies. When we review RWE submissions, we also look at those important factors.

So I will start with the data, fit for use evaluation. When we talk about fit for use data it means that data are reliable and relevant. Here the reliability includes accuracy, completeness, and traceability of the data and the term "relevance" includes the availability of data for key study variables, which include exposures, outcomes, covert, and also sufficient number of representative patients for the study.

In the early slides I showed different types of RWD and FDA does not endorse one data

source or another or seek to limit the possible source of data that may be relevant to answering study questions. So basically, many approaches can be acceptable and need to be evaluated on a case-by-case basis. So we encourage sponsors to communicate with the FDA early and often about RWE submissions.

So here are some examples about our fit for use evaluation. So I will use COVID-19 vaccine as example since most people in this audience are familiar with the COVID-19 vaccines. One potential source of bias when we use real-world data to evaluate COVID-19 vaccine is there is potential underreporting of vaccination status. Probably you still remember when the vaccine was first rolled out there were long lines in front of the mass vaccination site and no insurance information were collected. So basically, many people without vaccination code in the system may have received vaccines outside of the system. This underreporting of vaccination status could bias the result.

This example is the Moderna COVID vaccine post-marketing commitment effectiveness study. So we asked the sponsor to clarify how they handle this potential exposure misallocation, they mentioned that the data partner are receiving regular batch imports of external administration of COVID-19 vaccine. So the vaccination information in their system is thorough and as complete as possible in the pandemic setting, so this is an acceptable approach.

So here I want to show you another example looking at the same source of bias. Again this is exposure misallocation. And this is the Pfizer PMR safety study. And the sponsor, they propose several alternative solutions. The first solution they proposed is using a different type of study design. It's called self-controlled risk interval study where they only employ individuals who have documented vaccination, which means that the underreporting of vaccine status will know the biased result. It will only have an impact on the sample size. So the study will have smaller

sample size.

And another approach they propose is link to immunization registry. That is also acceptable approach because that would improve the accuracy and completeness of the data. The sponsor also proposed another study, a cohort design with historical unexposed comparatives. Basically using individuals before the vaccine is available. So we know that all the individuals in the historical comparator arm, they are truly unvaccinated. This would solve the issue about potential exposure misallocation. However, because that is historical control, then the period of those studies is different from the treatment arm that could potentially impact by time variant confounders. So here I want to mention some time variant confounder.

Again I'm using COVID-19 as an example. The COVID-19 pandemic, it could impact the healthcare access and health-seeking behavior over time. So, again, this is the Moderna COVID-19 PMR safety study. In order to understand the

potential bias from time variant confounder, the sponsor, they proposed using medical conditions that are not related to COVID-19 vaccine to test the temporal trend. So those medical conditions can also be called negative controls. Because healthy behavior could have different impact on mild, moderate, and severe conditions, you can see that the sponsor proposed several medical conditions with different severity over a different time period: Before COVID-19 pandemic, during the pandemic, but before vaccines available, and also after vaccine available. So these will help the sponsor detect the temporal trend and the potential time variant confounder. So this is also an acceptable solution.

When we look at fit for use data, outcome misclassification can be an important concern. Again, I'm using COVID as an example because sometimes COVID -- there could be COVID-19 outcome outside of the system. So for Moderna COVID-19 PMC factory studies, the sponsor mentioned that the data partner will ask patients

about the positive tests conducted outside of the system and the document in the EHR with internal diagnosis code. And also they perform chart review. Chart review has been considered as a gold standard that can help to validate the accuracy of the test. So this is also an acceptable solution.

So you can see that for our source of biases and fit for use evaluation, actually many approaches can be acceptable. Again, it needs to be evaluated case by case. And so we encourage sponsors to communicate with FDA early and often.

Here I want to show you another case study. This is a very rare disease, very different from COVID vaccines when you see millions of millions of vaccinees. So for this rare disease, there is an unmet need and the sponsor, they propose axonal controlled trials. So for the treatment arm they combined several clinical trials as well as expanded excess program in EU. And they have a natural history study used as a comparator arm, the untreated arm. In order

to make the treatment arm comparable with isolated control arm, the trials and also natural history studies are conducted by the same clinical team at the same clinical center. Also, in addition, though, to the natural history study, they also have untreated siblings compared with the treated trial patients.

This can provide additional evidence. So you can see that in these particular submissions, real-world evidence used as substantial evidence to support pre-licensure regular decision-making.

So as I mentioned earlier in the presentation, when we look at RWE record submissions, there are multiple key considerations. We first look at the fitness for use of the data. The data need to be reliable and relevant. And then we look at the trial or study design. They need to provide adequate evidence and also minimize bias in the descent stage. We also look at statute analysis to see where they can adequately control for bias in the analysis

stage. At the same time, the study comes back into meet regulatory requirement. And again, this is a case-by-case evaluation. There's no one size fits all solution. We encourage the sponsor to communicate with FDA early and often.

Well, thank you for listening. And I would like to thank my CBER/CEDR colleagues as well as our federal partners and collaborators. Thank you.

DR. TENNANT: Thank you very much, Dr. Lu. So we have time to take some questions. And thank you very much to the speakers for responding to questions in the chat. But I wonder, Dr. Mahler, if you could address as a question about how the PI treats complex allergens versus simple defined chemicals. If you could address that question, please.

DR. MAHLER: Sure. Thank you. So the process per se is similar to chemicals. However, the batch-to-batch consistency, it is less strict required. So this is a natural product and there is more flexibility and a higher tolerance for a

batch-to-batch consistency.

DR. TENNANT: Great. Thank you.

DR. MAHLER: But the process is basically the same. Yeah.

DR. TENNANT: Great. Thank you. There's another question for you. I don't know if you can answer this. What is the estimated cost for obtaining approval for one allergen?

DR. MAHLER: So there is quite a difference amongst the European member states. In Germany, approval of one patch test allergen is between 1,250 euros and 2,500 euros. So this is a special rate for patch test allergens or for test allergens in general because the regulators have quite recognized that with the test allergens there is not a big revenue to make for the manufacturers. So since 2018, PEI grants price reduction of 75 percent down to 25 percent, which is the 1250 to 2500 euros.

DR. DeKOVEN: Is that just for payment to the regulatory authority and does not include what the cost is to the manufacturer to make --

DR. MAHLER: Sure.

DR. DeKOVEN: -- sure we meet approval?

DR. MAHLER: Sure. So this is the fees --

DR. DeKOVEN: It's a big difference.

DR. MAHLER: This is -- yeah, so this is the regulatory fees for a marketing authorization In Germany. Of course, the development on the side of the manufacturer is quite higher. That is clear. But this was not the question, actually. I think this, we all agree.

DR. DeKOVEN: That was my question, the estimated cost. So because I think that's -- the material cost is what's the cost to the manufacturer? Regardless of what the cost is from the regulatory authority, if the cost is prohibitive, there will be no new topical allergens available.

DR. MAHLER: So I agree. I agree. So, also, a topic to raise is reimbursement. So we have heard earlier about the situation in the U.S. That there is fewer and fewer patch test clinics.

We have the same situation in Germany that patch testing is per se, not very attractive compared to cosmetology. And this is a matter of reimbursement. So, of course, this is medical -- medicinal products and they have their cost. And also the treating physicians need to be reimbursed adequately. So this whole system is viable. Yeah, sure, I agree entirely. I'm with you.

DR. TENNANT: Thank you. I think most of the questions seem to have been addressed by the speakers.

DR. RABIN: Yeah, there was one for me about how we calculated specificity and sensitivity. And to tell you the truth, I am not -- it was a while ago and I didn't think of the question beforehand, but I believe, and I'll simply, you know, have to follow up on this, but I believe what we did was we basically used the Finn Chambers as a gold standard. And so, you know, agreement and negative and positive with sensitivity and, you know, disagreement with specificity. I think that's how we did it. And,

you know, I'd be interested -- I would be very interested in hearing whether or not, you know, the experts on our panel really agree with that approach. You know, whether or not, you know, we're willing to hear criticism that we may not have taken the best tactic on that.

DR. DeKOVEN: You're right about for a TRUE Test, specificity and sensitivity, the comparator was the Finn Chamber.

DR. RABIN: Right, right.

DR. DeKOVEN: But I think the problem with new allergens is, you know, coming out in pet (petrolatum) (phonetic) or liquid, they're new. You know, there isn't a comparator.

DR. RABIN: Right.

DR. DeKOVEN: There's historical data typically --

DR. RABIN: Right.

DR. DeKOVEN: -- that's been done to determine what the best patch test concentration is --

DR. RABIN: Right.

DR. DeKOVEN: -- to minimize irritation and increase positive reactions. That's sort of the only thing we can do at this point.

DR. RABIN: Yeah. Which, you know, obviously, I guess points to the whole idea of the, you know, of the RI and the PR --

DR. DeKOVEN: Right.

DR. RABIN: -- you know, as surrogate numbers. And, you know, I think we understand that that may be the direction that we need to go to. I have to say, it's not very appealing to me, but, you know, but the perfect is sort of the enemy of the good. And I think that, you know, as we talk about in the next session, you know, the sorts of patches and the things that are available, you know, I'm very interested in hearing, you know, what the bars are, you know, in terms of, you know, what kind of numbers are really acceptable or not in that context. So I look forward to that. But I think that would be a better conversation after the next session when we hear about the products more comprehensively.

Sharon?

DR. DeKOVEN: I mean, I think it's critical, though, as you get, you know, as Jeff pointed out, this new allergen that was identified in the Libre glucose monitoring, isobornyl acrylate --

DR. RABIN: Right.

DR. DeKOVEN: -- had never been tested before.

DR. RABIN: Right, right.

DR. DeKOVEN: It was just assumed that it would cross-react with other acrylates, which it does not.

DR. RABIN: Yeah.

DR. DeKOVEN: It's a unique one.

DR. RABIN: Yeah. Yeah. No, that's -- it's -- yeah. And that's only going to happen more and more as, you know, obviously wearable technologies in particular are expanding.

DR. TENNANT: Well, I think if there are no more questions, we can end this session. Thank you very much to all of the speakers. And now

we'll be going to lunch and returning at 1:15.

Thank you, everybody.

(Whereupon, at 12:42 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:15 p.m.)

DR. TENNANT: Welcome back, everyone. Ron?

DR. RABIN: Yeah. Yep, I got it. So this is terrific. This is -- I want to thank everyone who has participated so far to what has really been a very informative day and I think will continue to be an informative day.

Dr. Erin Warshaw is going to moderate this afternoon session. And before she does, I just want to mention that for this afternoon session, even though we did have a little bit of a discussion topic for doctors, for those of us who are in the regulatory domain and Dr. DeKoven, who represented his regulatory domain, please feel free, we should participate in the discussion after -- that takes place after this afternoon's presentations because obviously, you know, the purpose of this discussion is to really, you know, think about -- you know, come to some conclusion to reach the goal of reaching some understanding

of how you think and how we from the FDI -- FDA can, you know, take a look at, you know, take a look at how we're going to deal with these products to get them -- to increase their availability to the patients who need them. And if some of this morning's speakers can contribute to that discussion, you should feel free to do so as well.

So, Dr. Warshaw, who will monitor -- who will moderate this session, completed her medical school training, internship, and derm residency at Emory School of Medicine in Atlanta. She served as the Minneapolis VA dermatology chief from 1997 to 2013 and completed a three-year VA Career Development Award with a master's degree in clinical research from the University of Minnesota in 2004. She's currently a professor in the University of Minnesota Department of Dermatology. She's a media director of the Park Nicollet Contact Dermatitis Clinic, a state-of-the-art tertiary referral center for occupational and contact dermatitis. She's held a number of VA and

investigator-initiated grants. She's mentored over 100 medical students. She has co-authored over 340 peer review publications.

So, Dr. Warshaw, take it away.

DR. WARSHAW: Great. Thank you so much, Dr. Rabin, for that very kind introduction. And it's really an honor and a pleasure to moderate this distinguished panel of experts who are going to comprise our discussion for this afternoon. We will have a significant amount of time after the presentations, as Dr. Rabin mentioned, for discussion. So, please, as the talks are going on or if you have a question from this morning's talks, please put it in the chat. And the presenters don't need to feel that they need to respond to those questions because we will have significant time afterwards for discussion.

So our first speaker this afternoon is Dr. Curt Hamann, who is president, CEO, and medical director of SmartPractice. He received his medical degree from Loma Linda University and has over 30 years of clinical experience in

contact dermatitis. In addition, he has led clinical and pharmaceutical development, registration, and manufacturing transfers of patch test allergens within the industry. He's a member of several European, North American, and Japanese academic and professional organizations in the field, and he speaks at many international conferences and seminars sharing his expertise.

So thank you, Curt, for sharing your expertise with us today.

DR. HAMANN: Thank you, Erin. Very kind introduction. Hey, can't see me. I can see myself here. Is my image up, folks?

SPEAKER: Not yet.

DR. HAMANN: Shall I turn it off and back on?

SPEAKER: Yes.

DR. HAMANN: Okay. And I also need my slides to be deployed. That'd be great.

Thank you, Dr. Rabin and the CBER team, for pulling together this public workshop on the Approval of New Patch Tests for Diagnosis of

Allergic Contact Dermatitis. I think it's super appreciated, very important for us to get a solution to this, and I hope that we can make some progress in our discussions with this.

And thank you for sticking around even though the government shut down. I recognize that that's above and beyond. So thank you very much. Next slide.

I have been tasked with continuing the discussion that we've had about creating sensitive and specific patch test allergens. A tall order, I think, in terms of the previous dialogue. I think just as a quick kind of introduction, I would say that an effective type 4 patch test allergen needs to be representative of the allergen to which the patient is exposed. It also needs to have effectiveness supported by clinical data. And then perhaps the most important, it has to have a defined identity, strength, purity, stability, and batch-to-batch consistency. Next.

I think to highlight, before we get into some of the details, the importance of preventing

as best as possible a misdiagnosis is a clear priority that I think we need to embrace. If we have a patch test allergen concentration that is too low, it will result in a false negative. If we have a patch test allergen that contains the wrong allergen, it may result in a false negative reaction or a positive reaction to an incorrect allergen.

I think a couple of examples there perhaps would be helpful. If you have a preparation for one of the titanium salts and it's contaminated with nickel and you tell this person they're allergic to titanium and they're not, that would be an egregious misdiagnosis. And it's possible. I think also when we have new substances that are being introduced, like the hydro peroxides, where the number of unknown compounds that are in these preparations that are now producing in excess of 45 percent positive test prevalences in patch tested populations, we don't know what we're testing to and I think that that is unacceptable.

If the patch test allergens contain unstable allergens or mixes, that could generate unexpected degradation products. It may also result in a false negative reaction or a positive reaction, again, to an incorrect allergen. And we're dealing with this right now as it relates to our preference at times as clinicians to have mixes, to be able to test multiple things simultaneously. And what we are learning is with the mercaptobenzothiazoles, you put four of them together and within a few weeks there's only three of them there. And one of the four is now in a higher concentration. So we could potentially have a false negative in somebody because of the change in that product on the shelf.

And I think it's particularly challenging when you cannot go to the literature or have a discussion with key opinion leaders and come up with a credible evidence-based estimate of how often this happens. Most of these patients are tested once and if the misdiagnosis occurs, we have no idea. And I think that is one of the

challenges that really reinforces the importance of knowing what's in the preparation and that it is stable for the full life of the shelf life on the label.

If we've got misdiagnoses, we've got the risk of over treatment, likely with the biologics, as we have heard, that are super expensive. And I think an increasing problem within this space. A delay in diagnosis and also an inappropriate management typically would be undertreatment. So we need to be sure that we're vigilant about prioritizing minimization as best as possible misdiagnoses. Next.

So we look at three different categories and I think we've kind of heard about them from the previous speakers in terms of how we're going to approach these. I think we understand that there's this core set of allergens that have been used for many, many years that we know a lot about. They're highly published and they are largely the same between countries and they kind of represent what we would call our standard

series. We've heard about it here in the United States as the American Contact Dermatitis Society Core 90 or the North American Contact Dermatitis Group Core 80. There are different other series at Mayo and we do at CDI here. Typically the cutoff there is a prevalence in the tested population of about 1 percent or greater.

And then we have this rare or uncommon category and that would be -- encompass a lot of these occupational allergens. And that is in a referred population where you would have prevalence of less than a half of a percent. And we think those need to get treated differently in terms of this development approach and how we prioritize them.

And then the third category we've also been talking about, which is these emerging allergens that, all of a sudden, out of the blue we have an insulin pump that's got a new adhesive in it. And we've got, you know, inflamed skin in patients that have got these pumps on their skin. And we're trying to figure it out and we need a

solution that doesn't take years. So we need a way to come up with a test that can be used by clinicians that maybe doesn't fulfill all of the ultimate regulatory requirements, but can at least get us down the road of solving the short-term problems. And if it does continue to be an important allergen, then move into the core allergen space and be subjected to the additional disciplines that it should have for a license. Next slide.

So this complicated topic of sensitivity and specificity. If we were to bring the statisticians on board, they would reinforce what we've already heard and that is that you must have a gold standard against which you can compare your new preparation in order to be able to calculate a true positive, false positive, true negative, false negative. If you do not have that comparator, you cannot do this mathematical calculation.

And I know we heard about it a little bit, that it is probably not a reasonable approach

to just try to compare preparations that are in a different excipient and think you can compare -- do the calculations of sensitivity and specificity with the same allergen in just different excipients. We think it needs to be a completely new model in order for this to be an approach that will solve our need to regulate these products.

Some of the things that are done clinically that I think have been helpful are just the reality of what happens if you use one of these preparations and you get a positive reaction and you inform the patient and they are very compliant in removing it from their exposure and they go into remission. That is a nice reinforcement that that patch test was effective for its stated purpose. And I think that can be a part of how we evaluate these.

And then on the reverse. We also have clinical opportunities for the repeat open application test where you confirm relevance of a positive by applying a small concentration to typically the antecubital fossa every day for a

few days. And if you can replicate the allergic contact dermatitis that was being experienced prior to avoidance, that would be a great confirmation that this is an effective test.

And then we did hear from Dr. Mahler that the collaboration between IVDK and the DKG and the Paul Ehrlich Institute in Germany came up with another approach to this that could help inform the clinicians and be valuable in the regulatory process using the positivity ratio and the reactive index. And I think that helps us particularly with the two extremes of allergens that are very irritating and those that have very, very weak positives. And while it's hard to get an absolute number of how that would define what is and isn't approved, it's very, very helpful in understanding whether or not the preparation of this patch test allergen is getting close to something that would be effective for a clinician. Next.

Patch tests are unique. I think we've heard that. I think it's important to

differentiate them in our minds from a therapeutic product. These are diagnostic tests. They're not for therapy. They are applied in very low dose for 48 hours on intact skin and typically they're only used once. So the safety dynamics and all that we are worried about with a therapeutic product we think needs to be modified in a risk-benefit approach to how these tests are used compared to a therapeutic product.

So this is particularly important because the majority of patch test allergens are not available as an active pharmaceutical ingredient in a typical way like it would be for a therapeutic drug. So it's a very, very different chemistry. It is molecules that are available in the everyday environment of our patients, whether it's a preservative in a personal care product or accelerator in the rubbers or resins, metals, et cetera. Very, very common, but they are not a traditional API and we think that's important to differentiate. Next.

Some other considerations I think to

this core group that we're talking about that we need these licensed, regulated, and available for use in all of the respective markets that they are desired. The approach we think is to begin initially with a review of the patch test literature and see which allergens that are in that core space have data that is clinically useful for the PR and RI data perhaps and significant numbers of case reports and series that are useful in this well-established use defense that they have been -- used effectively for 10 years or more. And that would be where you kind of begin. And that would inform often what is the excipient and what is the preferred allergen that is the most consistent representation of what would be exposed to the patient or what excipient is best.

If that isn't in the literature, I think that we have supported, and you heard a little bit about this from Dr. Mahler with the isobornyl acrylate, that you do a combined phase 2/3 small clinical style that compares these excipients and

concentrations. We think it is also important to have the two population groups, one with and without suspected ACD. And that will help inform on a quicker basis what is the best formulation.

We think it's important to favor the lowest irritating option. This is particularly important with some of the metal salts. Many of the metal salts have also -- also contain free acid in small concentrations. And if you get a pH below 4, it will be an irritant risk. And ideally, we try to keep it in that 4 to 7 range.

We also would like to favor options with chemical characteristics that are most likely to penetrate through the skin. This is one that we've worked on a lot as it relates to some of the metals. The great example would be testing with titanium dioxide. We do not think this is an appropriate test substance for identification of a true allergy to titanium. The dioxide has been chosen and is in ubiquitous use and toothpaste and all sorts of topical medicaments because it doesn't go through the skin. So the idea that

that would be chosen as the preferred diagnostic allergen for an allergy to titanium we don't think would be a good approach. So make sure that these things can get through the skin.

Favor the most stable option. Many of these substances, they either evaporate or they polymerize or they degrade or there are changes in them. And it would be important to identify the most stable option as the preferred choice. And then, as we've already said, favor substances that represent the patient's exposure. Next.

So we think that to have this sensitive and specific test that's effective, there has to be a significant investment in making sure that there are validated analytical methods for the raw materials. This is especially important as the majority of these patch test allergens aren't manufactured in a GMP facility. So that when you receive it, you haven't got the benefit of a GMP audit that tells you that it's done correctly. You need to have a receiving procedure that has a method to prove that what's there is there and

it's not contaminated by other things, that it's in a pure form that is something that will be not causing these misdiagnoses.

These methods need to be validated also for the finished product, to ensure that the identity allergen strength and impurity are still in place when the product is through the manufacturing process and ready to begin the stability studies. These manufacturing methods need to be qualified. It's amazing what can happen when you manufacture these, whether it evaporates or whether you end up having crystallization occur, things that you would not anticipate if you were not really investing in qualified manufacturing methods. And then there has to be a, you know, a stability indicating analytical method to make sure that you're checking of the ongoing stability of the products is consistent with what's on the label.

And this has been humbling for us because as we have integrated these disciplines into the business, we have discovered that nearly

30 percent of the marketable allergens in Germany, they're not stable at room temperature for 12 months. And that is indicative of the importance of why we need to be sure that we have the analytical methods in place. They evaporate, they polymerize, they crystallize, they hydrolyze, and even some of them are photosensitive through the syringe in which the petrolatum is placed. Next.

So when we look at what we've already heard about as it relates to how we approach this, the requirements for the quality data are fairly similar between what you've heard from Dr. Vera in the EU. Certainly that is being embraced in Italy and in Spain now. There is congruence with what the FDA is asking for, where there is an expectation of comprehensive quality data for each individual allergen that demonstrates the identity, purity, and potency. And we heard that the Canadian model, it's just four licenses with one representative allergen dossier per -- for each of those four. And the disciplines that we've just discussed are not in place before these

allergens are distributed. So it's very limited. Next.

And then if we look at the requirements on the clinical side, this is where there's been a differentiation between the EU and the United States. The USA has still preferred a phase 2 to make sure that the right dose in the right excipient is chosen and then a further study for phase 3 that helps address additional safety signs. Whereas the EU for this core category of allergens that we're talking about, that are the primary ones that we're really desperate for access to on a regulated basis, are, at this point, being subjected to the well-established use bibliographic data support, together with, you know, what we already talked about with the PR and RI data. So we think that that's a balanced approach at this point for the core allergens and certainly different from none of this being required in terms of the dossier for each of these individual allergens submitted in Canada. Next.

So in kind of stepping back, we think it

is an unacceptable situation right now where it takes five to seven years, even more than that when you throw in COVID, to generate the adequate phase 2 and phase 3 clinical data that the CBER is now requiring in order to submit and review these allergens. This needs to be accelerated. These allergens need to be available to treat patients. So we believe there needs to be immediate change in the regulatory paradigm for these patch test allergens in order to ensure their availability.

And we like the model that CBER used for the type 1 prick test diluents (phonetic) 15 or more years ago, where there was a whole bunch of them in use and the data wasn't great and the FDA knew it and probably most of the manufacturers knew it, but instead of just withdrawing them all, they gave a timeline of here's what we need from you and if you can't provide it and demonstrate safety and efficacy, then we're going to withdraw them. And that process I think was a way to preserve availability, but still force the industry to comply with what was needed to get

these products to a level appropriate regulation.

So we recommend an approach that harmonizes what CBER is expecting here with PEI and IFA for the approval of these core allergens that are of critical importance to us now. And I think that it's fair for us to communicate that we have submitted a fairly detailed proposal on what that could look like and, hopefully, over the next months we will begin a process of trying to get more detail into what that could look like. Next.

So the emerging category that we talked about, the isobornyl acrylate example, I think in any given year we tend to find something that is emerging and we need something now and a different solution needs to be architected for that. And you have heard, as we already said, Dr. Mahler talk about that. It is, I think reasonable to get a, you know, a phase 2/3 small study with a suspected allergen or substance that's in a new device or drug or consumer product that can be used in patients using -- benefiting only from interim analytical methods and stability. And

then if it does, in fact, become something that is clearly of significant importance for it to be added to a standard series, then the additional disciplines that we would expect from a core allergen would then be integrated.

And I think that's what resulted in a solution that was reasonable for isobornyl acrylate. I hope the next time it's even a little faster where that can be accomplished. But I think we need something like that.

If it is an allergen at that point that does not emerge as justifying the investment in all of those analytical methods and manufacturing processes and stability. We think it probably needs to, for the moment, stay with a short-term availability on a compounded named patient basis, so that those that are treating these really unusual rare things still have something available to solve the patient's problem. Next.

So, in summary, I think these are the four takeaway topics that we think need to be addressed. We believe that we need to harmonize

the requirements for the clinical data for these core categories of allergens with the EU for patch tests using some modified, well established use approach so that we can make these available and the patients get the diagnoses they deserve.

Secondly, we think if it's in that category of an emerging allergen, use data from a small combined phase 2/3 study with suspected allergens and use these interim analytical methods for the stability for them.

Third, we think we need to adapt the CMC requirements. This is not a therapeutic drug. They need to be adapted, but we still need to be able to ensure identity, purity, potency of these patch tests, and get some wiggle room because many of these are very, very unique.

And then finally, we believe that this process of getting these allergens registered needs to protect their availability during that transition period as we register them, leveraging the well-established use data and these CMC requirements so that the public health does not

have lack of availability to what is needed.

Thank you very much.

DR. WARSHAW: Thank you so much, Curt, for that excellent presentation. Reminder just to go ahead and put questions in the chat. There are already some accumulating there. We will hold those for discussion after all the speakers. Our next speaker is Dr. Amber Breck Atwater, who is a nationally recognized expert in allergic contact dermatitis. She's the past president of the American Contact Dermatitis Society, a member of the North American Contact Dermatitis Group, member of many different organizations, including eczema and international dermatitis organizations. She is also the manager for the American Contact Dermatitis Society's Contact Allergen Management Program, which is designed to help patients find allergy-free products. She's also active in the journals Dermatitis and Cutis as an associate editor, and is currently in private practice in Virginia and also a clinical associate professor of dermatology at George Washington University as

well as at Duke.

So, Amber, thank you for talking to us today about the patch tests that are available in the United States, Canada, and the EU.

DR. ATWATER: Thank you. Can you see my slides?

DR. WARSHAW: Yes.

SPEAKER: Yes.

DR. ATWATER: Oh, you can? Okay, great. All right, great. Well, thank you so much for inviting me to speak today. I'm excited to talk with you about this topic. Today we'll talk about patch tests available in the United States, Canada, and the European Union. And I think you all have gotten a little feel for that already today. But I'll go into a little bit more detail.

So we'll start with the United States because that's where we're located today and that's what we're talking about. First, and you've heard this already today, we have available to us for patch testing, the TRUE Test, which you can see the three panels here on this slide. And

you can see here that there's 36 chemicals, one of which is a negative control. So we're able to test 35 allergens with the TRUE Test. And this is approved in the U.S. for people who are age six and up.

So the question you'll ask yourself as we go through these different panels and ways to test is why would we prefer to TRUE Test? Or why would TRUE Test be recommended? So many patch testers who do what's called comprehensive testing, who do this regularly at a high volume, do not use TRUE Tests. But those of us who need a quick application, those of us who need a known standard, a dependable product, need something quick, will use TRUE Tests. And those are the main reasons that dermatologists and allergists in the United States might choose this.

But why would we need to test more than just TRUE Tests? I just mentioned that many of us who patch tests at high volume do not use TRUE. Why would we need to test more than TRUE Tests?

Well, when we look at data, and this is

a study published by the North American Contact Dermatitis Group most recently in 2025, but from allergens tested in the years 2021 to 2022, when we look at that data, we find that about 50 to 60 percent of allergens are detected with TRUE Test alone. But what that really means for your patient is that at least 40 to 48 percent of allergens are missed with TRUE Test alone. And the reason for the two different numbers is that this has been calculated two different ways. So at a minimum, 40 percent of allergens are missed with TRUE Test alone. That means almost half the time your patient who undergoes patch testing with TRUE Test is not going to find their allergy. That's a big deal.

So when we look at performing patch testing, otherwise, we do what's called comprehensive patch testing. And Dr. Brod is going to talk more about this later. But some of the screening series that we might use, you've heard about already today as well, the one that you heard mentioned already today is what's called

the American Contact Dermatitis Society Core Series. And it's important to understand that those allergens change over time. And currently this exists -- this consists of 90 allergens. We'll talk more about that in a bit.

We also have what's called the North American Contact Dermatitis Group screening series that's used by patch testers in the United States and Canada. We have a number of screening series developed by patch testing manufacturing companies, which can let you allow to choose -- to test a smaller number of allergens, so we have the 50, the 65, and the 80. And then if you want to, you can make your own custom screening series. And someone mentioned Mayo Clinic screening series earlier. They have their own specific screening series that they'll work with.

So, you know, you think to yourself, sure, 80 or 90 chemicals, that should be great, that should be perfect. But I'm going to answer this question for you, why would we need to test more than just a comprehensive screening series?

Well, we look back at North American Contact Dermatitis Group data once again. And when we look at our data from 2001 to 2018. When we looked at that data, we found that almost 22 percent of patients had additional positive allergens. Twenty-two percent of the patients that we tested had allergens that weren't identified just with those at that time, 65 to 70 chemicals that were tested. That's a big deal. Twenty percent of our patients were not funding their allergens.

And so then we get to this concept of what's called "supplemental patch testing." Okay. So this is what we test in addition to a standard screening series at this time of 80 or 90 chemicals in the United States. And so there are a bunch of different panels that can be either developed or purchased for supplemental patch testing. These are just some of them. Why are these important? You know, you have a hairdresser that comes in, you need to make sure to test the correct chemicals for them. You have a patient

who works in a nail salon or has a potential nail allergy. You need to make sure to test your nail acrylate panel for them. You have a patient who has a foot dermatitis, and you need to make sure to test all the chemicals that are relevant that could potentially be present in their shoes. And just to be clear, this is not an exhaustive list of allergens that we need available for us for testing.

So what you see on this slide, and there'll be four slides that we'll look at here is the top 10 North American Contact Dermatitis Group allergens of the most recent publication, which was published in 2021 to 2022. And what I'm showing you here for these top 10 allergens from for 2021, 2022, and this is the most recent data that we have published, what you can see is that these top 10 allergens have not remained the same over time. Right? So I'm going to draw attention to the allergen in orange. This is nickel, 2.5 percent. This bumped up a bit in 2021, 2022, and this possibly bumped up, or we maybe became more

aware of it in this time period because we started testing to a higher concentration of nickel at 5 percent. We need the flexibility to be able to test natural allergens at different concentrations when it appears to be that we're going to be able to diagnose our patients better and more efficiently.

What you'll also see here on this slide is the allergens in green. So in 2005 to 2006, in light green, at the bottom of your screen, you see the chemical methylchloroisothiazolinone, methylisothiazolinone. And you see that slowly trending up over time until it stops right in 2013. Why did we stop testing that in 2013? Because we realized that in order to identify the very common allergy of methylisothiazolinone, we needed to test that combined chemical, MCI/MI, I'll call it, at a higher concentration. So just above that, in the darker green in 2013, you see, we're testing at a higher concentration. And then just to the right of that even deeper green, we start testing methylisothiazolinone alone in 2015.

We need to be able to test allergens at different concentrations and maybe stop testing specific allergens when allergens change over time. And the reason that happens is because exposures to chemicals and products change over time. And that may be regional, national, or international the way that these changes occur. Towards 2017 and later, you see a bunch of other allergens. And these are top 10 allergens that we start testing, and we need to be able to add these as needed for our patients in the United States.

This is similar data. This is number 11 through 20 for this 2021/'22 data. And I'm just going to highlight a couple of things. Up in the top left corner, we see a green color starting in 2005. This is neomycin. You see this trending down over time. It's still relevant to test because we see positivity of at least 0.3 percent in consecutive tested populations. But we do see that allergen trends change over time. And that's the important point for this data.

Now, the next three slides I find

amazing because -- I'm sorry, the next two slides, because these are top 20 allergens for other years. So different than '21, '22, we have a bunch of other chemicals that have been top 20 allergens over time. Allergen trends change over time, and we need to be aware of that in the United States and not be fixed on a very small set of allergens that we have available for testing for our patients. So you see the trends going up and down.

You can see that in this slide -- actually, the next slide, you can see that a couple of our formaldehyde releasers are going down over time. And that is because our exposure to formaldehyde and formaldehyde releasers in the United States and products is going down over time. So you can see in yellow diazolidinyl urea trending down over time. You see the -- in like the pink color towards the bottom, imidazolidinyl urea, another formaldehyde releaser trending down over time. These trends are important and relevant for our patients.

Now, we mentioned the ACDS Core Series earlier, and it's important to talk about the fact that the ACDS Core Series is not a static series either. So I just have three of the series mentioned here, but the series is updated by members of the American Contact Dermatitis Series -- Society on a regular basis. So you see here that we've had updated series in 2013, 2017, and 2020. And on the left side of the screen, you see our allergens, our top 90 allergens for 2020.

But what's the most Important here, and the reason that this is in small font, is this table. In 2020, and every time they do an update, we changed our allergens. We changed what was relevant and needed to be tested for our patients. You see the number of changes were made here in 2020 for that ACDS core series of 90 allergens.

So then you're going to ask, okay, how do you purchase or how could you purchase allergens in the United States? So I am going to mention company names. There are only two, and these are the two. So, firstly, if you are

purchasing TRUE Test, you will purchase that from SmartPractice. If you want to purchase what's called comprehensive allergens, you can purchase that from either of the companies listed here on this slide.

There are some individuals who purchase allergens from something called the SmartPractice Allergen Bank. And this is essentially a situation where you can write a prescription for your patient to get specific allergens shipped to you specifically for that one patient, and we can order that from SmartPractice Allergen Bank.

And then you're going to ask yourself, well, how many allergens can you purchase in the United States? So, firstly, we talked about TRUE Test. We have 35 allergens within that test itself. From SmartPractice, the company that you saw on the right-hand of the slide previously, on their website, as of October 2nd, they had 544 chemicals listed. For Dormer, which is this company on the left of the slide you saw previously, as of October 2nd, there were 475

chemicals. Caveat being for neither company is every chemical always available. There are sometimes back orders or pauses in production, so probably a few less for both companies available at any moment, but many more than 35 and many more than 80 or 90.

So let's move on to Canada. We heard about Canada from Dr. DeKoven earlier, so we are already familiar with that. But what would Canadians test if they're going to do a comprehensive screening series? They test similar to the way that we test in the United States. I changed the order a little bit for these screening series, but truly, most Canadians who do comprehensive patch testing will do something similar to what we do in the United States. And some of them use the American Contact Dermatitis Society Core 90 Series because many Canadians are a member of the ACDS.

You heard from Dr. DeKoven earlier that they do have approval for allergens. In Canada, they only have approval for allergens to be

purchased from one company, and that company is listed here. And so according to the president of Dormer Laboratories, recently I had a conversation with him about this, he said that in 2017, 539 allergens were approved for Canada. About 475, as I mentioned a moment ago, are listed on the website. And according to him, in addition to those 475, there have been requests for compounds not available for purchase. So people saying, I really want to be able to test this chemical for my patient. Are you able to provide this for us?

Going back, I just want to mention one thing. TRUE Test is not available for use in Canada.

Moving on to the European Union, we've heard a lot about this and so we'll talk about it. So TRUE Test is approved for 12 countries in the European Union and they're listed here. It's only approved for adults and they have 35 allergens approved, same allergens as TRUE Test which we have available to us in the United States.

In the European Union, there is some

variability as to what a screening series might look like. There are screening series available on the websites for the different companies that sell them. Different countries might have their own screening series. And then there might be specific research groups that choose their own screening series as well.

In the European Union, they are -- technically have access to Chemotechnique and SmartPractice allergens. Chemotechnique is a similar company to Dormer, which we have access to in Canada and the United States.

And so the most important point of this next section that I want to communicate with you, to my understanding in conversations with colleagues in the European Union, is that there are differences in allergen access across the European Union, despite the conversation that we've been having so far today. So I contacted a colleague in Germany, actually maybe about five or six colleagues in the same email chain. One responded back and said they were speaking for the

group and they communicated with me similar to what you heard earlier: Only allergens with market authorizations can be purchased from one company. And they said that of the 174 allergens with market authorization, it's their opinion that only 86 are currently obtainable. This is a lower number than what we have access to in the United States from a standpoint of ACDS standard screening series.

Now, I want to acknowledge that the number 174 is not the same as the number Dr. Mahler mentioned earlier of 167. And in a minute you'll see another number that I got from SmartPractice, but it's a similar ballpark for the three groups.

My colleague let me know that there is a legal exemption available to them, so that if they don't have access to these specific allergens that they want tested, they can reach out to other countries to get, if available. In this case, in Germany, they reach out to Italy when they need additional allergens. This can be quite a

difficult process, expensive, and not easy for them to do. Pharmacies can prepare patch test substances as well.

Now, I spoke with SmartPractice about this and what they said was that there are 169 allergens available with licenses and that 121 allergens that have temporary authorization, meaning they can get via pharmacy from Italy if they need to get access to those allergens.

When we look at Italy, my colleague communicated that they only have access to SmartPractice allergens. There might be some restriction for them regarding occupational allergen access. SmartPractice said that there are seven allergens available with licenses and that an additional 321 can be accessed through temporary authorization. In Denmark, according to SmartPractice, there are 442 allergens with temporary authorization. In Spain, a colleague communicated that they do have access to both companies' allergens. If they need specific products, patient -- personal care products, they

can be diluted by a pharmacy. SmartPractice says that there's 1 allergen available with license, an additional 321 allergens available with temporary authorization.

In Poland they predominantly have access to Chemotechnique allergens. They cannot get access to allergens that are pharmacologically active. So, for example, neomycin, gentamicin, corticosteroids, they'd have to order from a pharmacy. And they can prepare patients own products for patch testing. They do also have access to TRUE Tests there. And then my colleague in Netherlands said they had access to both companies.

This is the last country, Switzerland. They can get allergens from SmartPractice and a few from Chemotechnique. They can get most allergens but not all. And they can test patients' personal care products.

And that is it. Happy to take your questions later.

DR. WARSHAW: Thank you so much, Amber,

for that comprehensive overview of the allergens available.

Our next speaker is Dr. Bruce Brod, who is going to talk about comprehensive testing in the United States. He is a clinical professor of dermatology and director of the Contact and Occupational Dermatology Clinic as well as the associate dean of Continuing Medical Education at the University of Pennsylvania. He is also a past president of the American Contact Dermatitis Society as well as a section editor for our journal. He has contributed significantly to the understanding and management of allergic contact dermatitis, including writing several book chapters on the topic and has lectured nationally and internationally on patch testing.

So thank you so much, Bruce, for talking with us today.

DR. BROD: Thank you, Erin. Can everybody see my presentation? I'm just checking. Can everybody see?

SPEAKER: No.

DR. WARSHAW: No, not yet.

SPEAKER: We're seeing your Teams window.

DR. BROD: Okay.

SPEAKER: If you'd like, I could also share your presentation.

DR. BROD: Yeah. How about that?

SPEAKER: Yes.

DR. BROD: Great. All right. Thank you. Thanks, Erin. Thanks for having me. And today my goal is to share a little bit of what comprehensive patch testing is and why it's essential for diagnosing allergic contact dermatitis.

To put things into perspective, we see that every day, typically, Americans use approximately 12 personal care products. That exposes them on average to 168 unique different chemical substances on a daily basis. And then if you look across the board at our personal care products in the U.S., you know, shampoos, lotions, conditioners, that's 10,000 unique substances in

personal care products. That doesn't include the thousands more that people are exposed to every day in the workplace. So you can see the potential for skin sensitization is significant.

I show this book, Dr. Anton de Groot from Europe has cataloged over 4,000 potential contact allergens that have caused allergy in some number of patients. And we use this as a reference. And most -- so most of the allergens that have been cataloged and documented aren't commercially available.

Comprehensive patch testing is -- it's not just a test. It's really a detailed investigation. And so what we do, what I do in my clinic is we really take a deep dive with patients. We try to match the topical allergens that we use to test a patient to, to their unique exposure at home, at work, their hobbies. And yes, we typically in our patients use one of the comprehensive baseline series. At Penn, I use the ACDS core, NACDG, and we saw and Amber talked about other variants, but we also couple that with

supplemental panels. But this isn't done willy-nilly. It's done in the context of doing a very detailed exposure history with patients. We look at the rash, that -- where it is, the timing of the -- and the timing of those symptoms.

And so if we lived in a world without a broad array of relevant allergens, we're really going to miss diagnoses in patients and we're going to leave patients kind of stuck in a cycle that you see on the right where it's just going to be kind of guesswork and broad avoidance of allergens. Even with comprehensive testing, you know, there's still limitations, right? I mean, we're not going to get to perfect. And we talk -- you know, remember that number 4,000. So if you think about, you know, even a good comprehensive baseline screening series of 80 or 90 allergens, that's like 2 percent of known allergens. So, no matter what, we're operating at the tip of the iceberg. And that's why we need to be nimble and that's why we need access to broader panels because if not, and we miss the key triggers for

allergic contact, patients are going to suffer.

So I'll talk briefly, this is a landmark study that's well known to many patch testing dermatologists done by the NACDG, a retrospective that looked back about 43,000 patients, so a large cohort. And also on this slide I put the -- you know, just to elucidate the different supplemental series that we use at Penn. So at Penn, and our general derms, you know, still find utility in a quick screen using the FDA TRUE Test. But sometimes I end up seeing a lot of those patients if they're not improving for more comprehensive testing.

So this, you know, I'll talk a little bit about the landmark study from the NACDG, but basically to summarize that the results indicated, and we heard some of this before, that -- and this looked at patients tested to comprehensive baseline and supplemental series, that 22 percent of these patients had relevant reactions to supplemental allergens. And out of that group, about a quarter of them only reacted to

supplemental allergens. So, you know, the bottom line is just using standard panels without supplemental series is going to miss a fair number of relevant allergens. And then just looking into occupational allergens, 17 percent would have been missed without supplemental panels.

And this has been validated. This is a list and it's not all of the studies, but these are multiple U.S. and some Canadian partnership studies that have also looked at the impact of using supplemental allergens and what would have been missed. And the data is pretty consistent that more limited testing would miss around, give or take, 20 percent of the relevant allergens. So this is underdiagnosis and it would affect patient care.

This slide is really about best practices and the nuts and bolts of what goes on in a comprehensive patch test clinic. And I'll start by saying that an important part of patch testing isn't just commercially available allergens, but it includes testing the patient's

own products, leave-on products, when the product is under suspicion based on the location and the timing of the dermatitis. And so that might include, you know, lotions, hair products, hair gels in the neat form, but sometimes gloves, sometimes parts of shoes.

And we really do this for a number of reasons. One, to determine relevance, which ends up being high when the allergens that are positive on patch testing are in the product ingredient label. And another reason is, secondly, when there is negative correlation. So, you know, patient is positive patch test to a product, but negative to the individual allergens, right, because we don't have access to the entire universe of allergens. That leads us to take a deeper dive into the ingredients and the products and prompts us sometimes to obtain the commercially available allergens on the product label that we may have missed.

So the other component, of course, as I stated before, is choosing supplemental series

based on a very detailed exposure history. And that's really important for high-risk occupations like hairstylists, machinists, and healthcare workers. And if we look at kind of what the standard community of care among patch testers, as we can look at some of the data from these survey studies from ACDS members, these tend to be patch testing physicians, and you can see from the surveyed members, the majority of patients test to more than 81 allergens. So we see that comprehensive patch testing is common, but not everybody does. Right? There's still a practice gap and maybe there's more many reasons for those gaps, sometimes institutional barriers, you know, and other reasons as well.

And then in this slide from the survey data, we see that most ACDS members surveyed test either always or at least some of the time to supplemental allergens. So I'd like to shift and look at some real-world cases where access to allergens beyond the FDA approved 35 made a meaningful difference in patient outcomes.

And so we heard about MI, but I kind of want to take a little bit of a deeper dive into that. So we heard that MI, methylisothiazolinone, is a widely used preservative and a very frequent and relevant allergen. But it wasn't always tested separately. At one time it was only -- it's part of the FDA approved series and we tested it in combination with methylchloroisothiazolinone. And if that were to hold true today, we would have missed an entire epidemic of MI allergy, which in part is really still going on today, as we heard. So thanks to flexible access, when we started to see a signal for MI allergy, we were able to identify patients with this early on in the story, maybe not as early as we would have liked.

So as we look at this timeline, we see that in the '80s, MCI and MI was used commonly in combination. But there was a shift and industry started using it as a standalone product. And so the concentration increased by just 25-fold in personal care products. And had we just tested to

the MCMI combo because the MI concentration in that is much lower, we would have missed about 40 percent of the MI allergies because the concentration was too low. So our ability to pivot obtain commercially available MI as a standalone preservative at a higher concentration was key to recognizing and responding to this emerging epidemic. I'll show you a couple cases.

This is a 52-year-old with severe facial dermatitis, really debilitating. Patch tested the patient and you can see that there's a positive reaction to MI, methylisothiazolinone, and a negative reaction to MCMI, the combination. And the source was not difficult to determine. The patient was using a shampoo and you can see on the ingredient label the shampoo contain methylisothiazolinone. So this patient had improvement.

And another similar case, this was a 75-year-old with disabling hand dermatitis. I mean, these patients are cripples. I mean the hands are red, they're cracked, they're fissured,

they're bleeding. Patients, you know, can't open a jar when they have this. And again, you can see the patient had a positive reaction to MI, but a negative reaction to MCI/MI. And the source was the dish soap.

And so now today, MI is found in thousands of products and allergy has become so common and life-altering that there's actually a dedicated Facebook support group within thousands of members who have methylisothiazolinone allergy, you know, providing tips and tricks and sharing their stories. And I think this is really important because it underscores the real-world impact and why it was so critical we had access to this allergen.

And we talked about how patients really can't be their own detective because of the delayed type nature of contact dermatitis. And I think this really underscores that. This was a 62-year-old, who came to me with intermittent pruritic facial dermatitis for two years. And the patient, their correlation was it always occurred

after air travel. The patient did frequent air travel for business and believed that they were allergic to something in the airplane air filtering system, something like that.

But patch testing revealed acrylate allergy and we were able to link that to nail cosmetic products used before the trips. But, you know, a patient would go to the nail salon, have gel nails placed. We know it's a delayed reaction, so that wouldn't occur until several days later when the patient was already, you know, on the airplane or coming off. But you can see the patch testing confirmed multiple acrylate allergies, with the source being her gel nail manicures. And most of the acrylates that we test at Penn are part of the supplemental series, so we would miss this.

Acrylates from nail products cause hand and nail reactions pretty severely, so these are important to detect. We see some of the consequences. And you know, when the nails separate, that's called onycholysis. And we see

that with acrylate allergy to some of the porcelain nails, it affects tactile function and affects dexterity. And with the gel nail users, besides seeing reactions on the face, we see a lot of dermatitis and swelling around the nail folds as well.

And we really saw a spike in this during COVID, right, because nobody could get to the nail salon. So home acrylic nail kit use surged. And it was really important for us to be able to test patients to these acrylates, again, mostly in supplemental series. And it was a perfect storm, right, because, you know, patients were ordering these kits from online suppliers. These are potent sensitizers. We found out many of them were being trained on how to use these potent sensitizers, these home users, from social media. And so if acrylates aren't cured completely, they're going to be allergenic. And so, you know, we think a lot of these patients became sensitized, and they're still in use today in the United States. People can order these home kits

that are very popular, and so I think we're still sensitizing a lot of patients.

And as we saw, acrylates are common in all sorts of medical devices. And identifying these can be very challenging. It's often proprietary. We were able to identify IBOA and appreciate the manufacturers for making these commercially available, but there's others out there and we're not always going to be able to be so fortunate to identify these device allergens. But when we can, and we all from Dr. Yu's talk, it's really helpful.

Another case, this is a massage therapist who had chronic hand dermatitis. Patch testing revealed allergy to lavender. Lavender is an uncommon -- relatively uncommon on positive -- positive on patch testing. Massage therapists like aromatherapy. They put it into their massage oils. It's relaxing. And so this is a good example of both occupational dermatitis and botanical allergy. And you know, so this is -- these hands are pretty dysfunctional for somebody

who does massage therapy for a living. And patch testing revealed reactions to the patient's lavender, but also commercially available lavender oil.

And I think one of the takes critical messages here is the patient did not react to the standard fragrance markers like fragrance mix 1 and 2 in balsam of Peru. And that's often the case with botanicals. Even though they're building blocks, they have to be tested individually. And so where I patch test at Penn, I have several botanical supplemental series based on exposures.

Again, the standard fragrance mix in the approved -- FDA approved type allergens don't often detect botanical allergies. And there's a huge consumer demand today for all natural. Consumers really like using products that have botanicals in it. To identify these reactions because they are contact allergens to things like lavender or to tea tree oil, things like peppermint, we have to use -- we need access to

supplemental series to diagnose these patients.

And then the last case, this is a middle-aged patient who came to me with a widespread, highly pruritic dermatitis. And it happened after spinal fusion surgery. And the patient presented with this concentrated area of dermatitis on the lower back over the surgical site, but sometimes we see reactions become systematized. So this patient also had a widespread eczematous eruption, red scaly patches, couldn't sleep, really couldn't function like a normal person with really diminished quality of life.

And so the material used for the fusion included osteo screws with vanadium. And so patch testing was very helpful and very confirmatory here, revealed a reaction to vanadium coinciding with the metal used in the implant screws. We confirmed this with the orthopedist. And these -- vanadium is not on the standard series, so we wouldn't have been able to diagnose this at all. And removal of the implant, although not

immediate, after about six weeks, led to resolution of all these symptoms.

So, hopefully, that's been helpful to kind of give us a real-world feel of the impact of supplemental testing. And I'll conclude by saying when you do comprehensive patch testing, this is really a type of personalized medicine. I think patch testers were doing personalized medicine before it became a thing. And I'll say that nearly 60 to 70 percent of our patients improve with targeted allergen avoidance after comprehensive patch testing. So basically testing to 100, 100-plus, or more allergens based on history when indicated, helps us tailor avoidance to those exposures and leads us on a journey to begin to find a cure or improvement in those patients. And, you know, the whole test takes, you know, anywhere from 72 to 96 hours. It's practical, it's a personalized diagnostic approach, and it delivers better patient outcomes.

Thank you.

DR. WARSHAW: Thank you so much, Bruce,

for that great talk. Our next speaker is Dr. Luz Fonacier, who is a professor of medicine at NYU, where she serves as head of allergy as well as the training program director. She is unique in that she completed residencies in both dermatology and internal medicine, followed by two fellowships, one in allergy and immunology and the second in dermal immunology. She's the past president of the American College of Allergy and Asthma and is the chair of the American Board of Allergy and Immunology. She has published 20 textbook chapters and many journal articles. And because of her training in dermatology, allergy, and immunology, her special interest is in the dermatological manifestation of allergic diseases. And she's going to talk on alternative diagnostic tests for allergic contact dermatitis.

So thank you.

DR. FONACIER: Thank you, Erin. I am having difficulty putting this in the mode for presentation, but I can actually advance it from here. So if it's okay with everybody, I will stay

on this mode. So my topic is a little bit --

SPEAKER: We can see it just fine.

DR. FONACIER: I'm sorry?

SPEAKER: It's perfect. We see it just fine and we can hear you.

DR. FONACIER: Okay. Thank you. So it's a little bit different. Everybody's been talking about the patch test and during this whole morning and then a half of this afternoon. But my topic is what if you cannot patch test? What are the alternative approaches and actually what is the gold standard?

So these are my disclosures. My research goes to the NYU Langone Hospital and I'm on advisory board in some other pharmaceuticals.

So I would like to discuss alternative approaches to the diagnosis of allergic contact dermatitis and two possible scenarios. One is prior to your doing the patch test and the second is if the patch test cannot be done. But there are, as we have heard already, many barriers to patch testing. One it's a time-intensive process.

It takes three visits, the application, 72 to 96 -- removal at 48 hours, and then you have the 72 to 96 hours. The second is cost and insurance coverages, availability of service, and finally, I think very important, is geographic limitations of the providers. There are really very few good patch test areas in many parts of the United States and around the world as well.

So the first thing that actually patients do even before they come to your office is an empiric allergen avoidance. This could be patient-driven or physician-driven. When the patient tries a product, they had a reaction, then they kind of know what it is and they remove it. So on their own they will change, they will eliminate, they will avoid products. And they also would like -- they think that hypoallergenic products will eliminate most of the allergen, but the patient thinks that natural is hypoallergenic. As an allergist I always say, oh, yeah, you know what? Poison ivy is also natural.

So patient -- physician-driven will be

based on history and the physical exam. The physician needs to do a detailed physical history and of the product use, occupational and hobby exposures, topography, location of your dermatitis. Consider, at least for us, allergy is very important, ectopic, airborne, and concert contact dermatitis. And finally, if the patient does improve, consider reintroduction of the products.

There are very many disadvantages for doing this. One is the cost of hypoallergenic products. They are more expensive than what the over-the-counter products are. Second is acceptability of these products. I mean, they're not as accepted by the patient. There is also unnecessary avoidance of products that the patient is not allergic to. The fourth is the labeling issues that not all labeling -- not all the ingredients in the product are put in the label. There's a difficulty in doing this if you have a generalized contact dermatitis. And finally, by doing empiric avoidance, you are unable to really

identify the culprit allergen.

So the presentation of contact dermatitis, as we said already, you know, is location, location, location. And really these are the most common location. And this is where the patient will be trying to avoid whatever contact allergen they are suspecting. And we published this in the annals, and these are the things that are likely products, depending on the patient's distribution of dermatitis. And you can see it is pretty difficult to avoid these products. There are many products to be avoided to -- actually in facial dermatitis. And if you look at the lip dermatitis, although there are some clues as to whether it's top and bottom or both sides or upper or lower, you still have many products that you need to avoid. And even in the lip dermatitis 3, the most common cause is an irritant contact dermatitis, like in (phonetic) allergic contact dermatitis.

Now, it even becomes more difficult when you have a scattered generalized dermatitis

because although the most common is textile, formaldehyde resin will also be a common allergen. This is when, in the hospital, the new uniforms that are shrink-free and wrinkle-free was issued and most of the -- some of the nurses and physicians developed this generalized and even spotty contact dermatitis.

What about the use of low-contact allergen products? So there's a recommendation prior to patch testing to eliminate the most common allergens. And the most common allergens would be fragrances, formaldehyde resin, non-formaldehyde resin. For preservatives, we heard about MCI/MI, Lanolinko cocamidopropyl betaine, then sulfanone (phonetic) 3 and paraphenylenediamine. And I just use the CAMP site to generate something I will give the patient prior to patch testing. If they are allergic to the most common group of allergens, it might help. But still, they will need a patch test to identify.

There is a pediatric preemptive

avoidance strategy in pediatric allergic contact dermatitis. They called it P.E.A.S. This was published, that allergen avoidance of these common allergens in children. It's estimated that a third of children with contact dermatitis would potentially benefit from this low contact allergens.

Unfortunately, it is difficult avoiding the most common allergens. So the traditional approach is we give the name of the allergen, the patient's asked to review package to identify the products free of these allergens. However, these typical allergen names are really long, difficult to spell, commonly have numerous complex synonyms, and often very intimidating for the patients. Thus, the compliance with allergen avoidance is really frequently difficult.

For metals, what are the alternatives for patch testing? So in metals there is such a thing as lymphocyte transformation test. Both the practice parameters in allergy and the ACDS really say that the lymphocyte transformation test is not

widely available. It's also subject to variability. You only have about eight different allergens that you can test in the blood and it has a rapid decay of T cells. Remember that you will need live T cells for these tests to come up with a positive test. And transport is important for this test.

It can be useful in a few questionable cases. So, for example, there's a data -- there's a publication where you have a negative patch test, but persistent concerns of metal allergy. Fifty-four, 56 of these patients with titanium implants had a negative patch test, but a positive lymphocyte transformation tested titanium and those symptoms resolved after implant removal. So this is a case series where the lymphocyte transformation test may be useful.

There are other investigational procedures that are not patch tests. We have investigations on intradermal testing with metal salts. And you have the local lymph node assay for metal allergenicity. Again, they are not

ready for prime time. These are all just on the investigational process.

There is a move to detect culprit metals if one is known to avoid contact -- is known to be allergic to them. And so for these two metals we have the nickel spot test, which is a dimethylglyoxime test, and the cobalt 2-nitroso-1-naphthol-4-sulfonic acid to detect actual allergen in the metal to prevent contact with the patient with a known allergy to them.

This has been discussed a little bit, which are the repeat open application test and the use test, where you apply your product on the antecubital fossa and retro auricular for facial dermatitis twice a day for about 7 to 14 days. And you look for any irritation or redness, erythema, or papules. If you have a positive in 15 to 30 minutes after the initial application, consider contact urticaria. But if you are thinking of contact dermatitis, you can have delayed reaction. You can reproduce that usually in 7 to 14 days.

The absence of a reaction does make contact dermatitis unlikely. The use test is the application of the product suspected to the actual area used as the same way as when the dermatitis developed to prove causation. For example, a facial cream 1-by-1 centimeter area on the face would be considered a use test. The repeat open application test and the use test cannot identify specific causative allergens, but can allow patients to determine which of their personal care products are actually causing reactions and which they can use.

The use of barriers can help prevent contact dermatitis, so you have gloves in patients with hand dermatitis. And there is very conflicting data on the use of protection creams. And the conclusion is that taking all of these secondary outcome measures together, the main result of the study is that skin protection cream alone have very small effects on the skin barrier in workers. This is an occupational dermatitis in building and timber industries compared to skin

care alone or in combination with skin protection. Another study concluded that the generally recommended skin protection regimen seemed to provide effective prevention of occupational skin diseases in some occupations.

Finally, there are government regulations to actually avoid sensitization and even decrease exposure of the patient. So in EU, nickel imposed assemblies inserted in the pierced part of the body, the nickel release should be less than 0.2 centimeters squared per week. In articles in direct and prolonged contact with the skin, nickel release should be less than 0.5 centimeters square per week. In Denmark, there's also a nickel derivative where the Danish Ministry of Environmental Statutory Order Number 472 limits the nickel in products, and this is also the same in China. Unfortunately, we do not have such directives in the United States.

For methylisothiazolinone, in the EU, they restrict MI in rinse-off products; maximum allowed concentration of 15 parts per million

(phonetic) in these products. And p-phenylenediamine in the EU limits the maximum concentration and requires warning labels.

So in addition to all of what I said, in place of patch tests, prior to patch test, or prevention of sensitization, the truth is the relief of symptoms average 143 days sooner on patch tested patients as against non-patch tested patients. And the diagnosis of allergic contact dermatitis made solely from history is truly under suspected, underdiagnosed, or even misdiagnosed compared to those patch tested. The identification and avoidance of contact with offending agents is still the key to the success of irritant and atopic allergic contact dermatitis. And still I think Coleman's 1982 statement is still true, is that the greatest abuse of patch testing is still the failure to use the test.

There are some useful resources that I included in here. And thank you very much for allowing me to participate in this great workshop.

DR. WARSHAW: Thank you so much Luz for that really outstanding presentation. Our next speaker is going to talk about "Gaps in Allergic Contact Dermatitis Patch Testing." And that speaker is Dr. Alex Flamm, who is an associate professor of dermatology at NYU, where she practices not only dermatology, but also dermatopathology. Her clinical focus is -- in clinic is on contact dermatitis. She is president elect of the American Contact Dermatitis Society as well as a previous board member of the Society. She is an associate editor for several dermatology journals, including JAAD and Cutis. She received her medical degree from Mount Sinai and did her dermatology residency at SUNY Downstate. She's authored numerous publications and textbook chapters and has multiple institutional and national awards for her teaching and volunteer work.

So, Alex, take it away. Okay. Alex, you might be muted. As we're waiting for that presentation to come up, please go ahead and put

any questions or comments in the chat so that we can have a robust discussion after the presentations. Just checking on the FDA folks. Do you have Dr. Flamm's presentation?

SPEAKER: Yes.

DR. WARSHAW: There we go.

SPEAKER: She said that she got off. She somehow got taken off the site here, so.

DR. WARSHAW: Oh, okay.

SPEAKER: I don't know. Just if somebody can keep an eye to see if she's trying to get back in.

SPEAKER: We definitely show (phonetic).

DR. FLAMM: All right. Can everyone hear me and see me now?

DR. WARSHAW: Yes.

DR. FLAMM: I tried to share my screen and then I got kicked off. I don't know if you guys are trying to tell me something. You want to finish early maybe. Looks like you already have my presentation up. So why don't we just start with the presentation that we have up over here

and we'll get started.

All right. So to end things off, I guess, with a bang is probably the best way to put it since we had to have a little bit of technical difficulty over here. My name is Alexandra Flamm. I am an assistant professor of dermatology at NYU. And I get to end off here by talking about our current gaps in patch testing.

So what I'm going to say is really what I am going to do here is I am going to be trying to raise questions and speak about what I think is a pretty challenging topic. I don't think what I'm going to be bringing up is particularly new. I think a lot of my colleagues who have spoken have spoken quite eloquently around this. But what I really want to do is start our discussion and to really think about what we need to address in patch testing as we go into our crucial Q&A after this. So let's go to the next slide.

All right. So in order to think about what our gaps in patch testing are, we really have to think about what are our guiding principles.

So what do we need in order to ensure high-quality care to patients? So, again, this is patient-centered care, so we want to be thinking about access. So if our patients don't have access to patch testing, then what are we doing here? Next is making sure this is high level, personalized medical care for our patients, the flexibility to respond to those new and emerging concerns and allergens that may come up. And in the end, what it's really all about is leading to improved quality of life. So, next slide.

So I'm going to bring up a patient over here. This is one of my patients. You can see on the left side, this is where we started, hands that were cracked, that were bleeding. This patient wasn't able to go to work because of all of these open sores. He was out of work for days or even weeks. And this is where we were at the end on the right-hand side, completely clear, able to go to work, able to do the activities that he enjoyed from day to day. So as I talk, I really want to make sure that we're really centering this

on the patient. As a clinician, as an educator, I think this is really where our value lies and what we need to do in order to ensure high-value patch testing. Okay. Next slide.

So, again, let's talk about those four guiding principles, and then let's talk about gaps associated with them. All right, next slide.

Perfect. So access is our number one. We touched upon this a little bit earlier in our session, but I really want to dive into this a little bit more over here. Okay. So let's go to our next slide.

So when we talk about access, there's lots of different things we're thinking about. We're thinking about access just to patch testing in general. We're thinking about access to comprehensive patch testing, and also just thinking in general about ensuring that we have access to allergens in order to perform both any patch testing and comprehensive patch testing as well as. Let's move on to the next slide.

All right. Access to patch testing.

Let's go into it. Next slide. All right. I want to go into some data. We don't have very recent data, but I want to highlight some of the data from the previous decade in order to talk about where we are right now in terms of our access. And when you look at the provider numbers and the physician numbers, those who are doing any patch testing, it's increasing, but it's still persistently low, especially in our rural areas. If you look at some of this data in terms of counties with a dermatologist or with any provider offering patch testing, you can see that maybe in our metro areas we're up to 20 percent or so of counties. But then when you're looking at your rural counties, really any provider offering patch testing, about 1 percent. That means that we have patients that are driving hours or traveling hours in order to get patch testing done, or they're just foregoing it. So this is an area of tremendous need. Next slide.

And let's talk about the average number of allergens being placed. So this has increased

overall. So you can see in terms of average numbers of patch test per beneficiary among both dermatologists and among all physicians, we're moving up. We're getting closer to that 80. But that average is still not what we've reached at this point in time for comprehensive patch testing. And again, you can see a market divergence where you're seeing more patches being able to be placed in more metro areas and it's going to be lower in our non-metro areas, showing that some of our rural areas in the country really don't have access to comprehensive patch testing. Next slide.

And again, that comprehensive patch testing, looking at it, even diving in of greater than 80 or more, it's going to be not as much as we'd like. And I think these numbers are -- you know, they speak for themselves. You can see that in terms of percentages, we're talking about low single digits over here. Next slide.

And then just talking about patch testing availability throughout the entire

country, not just metro versus non-metro, but regions of the United States. You can see that there's significant variability in regions of the U.S., which -- what percentage offer patch testing. So we're seeing that, again, there's lots of divergence in terms of the type of patch testing that's available depending on where you are in the country. Next slide.

So really diving into access. What we need to make sure that we have and what we need to identify is, first off, access to physicians who can accurately identify when there is possible allergic contact dermatitis. So even before you get to patch testing, you need to make sure that you have a clinician that can look at the cutaneous findings, so look at the rash and say, you know, I'm worried this might be allergic contact dermatitis based on what I'm seeing, based on the history, to understand when patch testing is needed as a good next step, and to be able to educate appropriately to patients, hey, I think you might have allergic contact dermatitis, and be

able to diagnose its etiologies overall.

So we might think this is, you know, very basic, very straightforward. But in our patient testimonials earlier, what we heard was that many of these patients had to see multiple physicians, multiple providers, until they got to that one that said, hey, I think you have allergic contact dermatitis and I think you need patch testing. So this is definitely one area that we have gapped overall. Next slide.

And then additionally, like we said, patch testing access. We need to make sure that we have access to physicians and the patch testing centers that can perform patch testing, make sure that there's appropriate placement of allergens, make sure there's correct interpretation of patch testing, and to provide patients with appropriate educational materials. And I think the correct interpretation is so important because we talked about earlier in the session the idea of misdiagnosis. And misdiagnosis may have to do with, you know, the types of allergens that are

placed, the concentrations, the purity, and I think that's a great area for discussion. But misdiagnosis also comes from misinterpretation. And so we need to make sure that we are educating physicians on the correct interpretation of patch testing. Next slide.

And then comprehensive patch testing access. That's everything we talked about in terms of patch testing access, plus making sure we have access to comprehensive panels of allergens, that 80-plus, those supplemental panels, making sure we have those to accurately diagnose exposures. Next slide.

And then let's just talk about allergen access. And we've really talked that this is a real key area of need. It's really important that we have stability of access to our current allergens, which we know have been critical tools to correctly diagnose allergic contact dermatitis. But also to note that we have that flexibility and ability to incorporate new allergens as they come up, as they emerge. Next slide.

All right. Let's move on to our next gap. So we'll click ahead over here. So let's talk about personalization. Next slide.

All right. So when we're talking about personalized medicine as it relates to allergic contact dermatitis and patch testing, really gaps in areas we need to focus on are real-world data. And we had a really good talk earlier about real-world data versus real-world evidence, so I'm not going to dive into that as much. Talking about the idea of best practices we should follow in order to ensure high-level patch testing. And again, making sure that there's access to customizable testing, knowing that each person's exposure profile and allergen profile are completely different. Next slide.

All right. Again, let's talk about that real-world data. So what we're talking about is, you know, in gaps that we want to think about is where is the location of this data? Where is this coming from? Is this coming from international data or is this U.S.-based? We know that the U.S.

Is unique. It has a unique patient profile, it has unique manufacturing practices, unique types of products they're exposed to. So being able to have data that's U.S. based is going to be really important. And as we talked about, there's that idea that there's a lot of regionality in terms of allergic contact dermatitis and access to patch testing. So ensuring the data we're drawing on come from all regions of the U.S. and not just from specific areas.

How comprehensive is the data that we're drawing on? You know, there's a lot of different practice patterns when it comes to patch testing. We need to be looking at practice sizes, practice types. Where are they located? Again, that's that urban metro area versus our more rural areas. The types of physicians who are doing the patch testing.

And then when you're delving into the data, how is that being pulled? Is it based on claims or is it based on other types of data? All of this is going to be important in order to

ensure that when we're looking at our patch testing recommendations, we're drawing on data that's very much reflective of the U.S., which is a blend of a lot of different backgrounds, a lot of cultures. Next slide.

All right. So, again, those best practices. We need to draw on what we currently have, who is going to determine these, how they can best guide patient care. We have our established national societies, things like the ACDS, we have the NACDG, we have large academic centers and comprehensive patch testing centers that are leading the charge on this. But we need to know how we can incorporate all of this, again, in order to ensure that we have high-level patch testing. Next slide.

All right. So where else maybe have some gaps we need to focus on? Let's click ahead over here.

Again, let's focus on flexibility, which is something that we've talked about quite a bit during this session, but I think is important to

still touch on. Next slide.

All right. So when I talk about patch testing flexibility, I think about both elasticity and flexibility. What that means is that we have an ability to respond to those changes in prevalent allergens, response to new products coming onto the market, and also a response to new manufacturing techniques that are emerging in order to create this product as well. And I think this is quite important in particular for our patients with occupational dermatitis, too. Next slide.

All right. So I think that Dr. Atwater really talked about this in detail in terms of the allergen shift, so I'm not going to spend as much time on this. But this looks at the NACDG 2021 to 2022 patch testing results. And I think this table is really important because it focuses on the percent positivities for that 2021 to 2022 cycle, but also compares it to previous cycles all the way back down to 2011 to 2012.

Let's click ahead over here because

really what this is going to focus on is, for instance, we have some allergens like nickel, which are high and have stayed high over the past couple years. So we can click once to show that current positivity for the 2021 to 2022 cycle. And then clicking again, showing that relative comparison that this has stayed toward the top of our allergens of concern. Next click over here. It also shows the MI story, which, again, we've talked about quite a bit over here. And you can click ahead showing that it still stayed relatively high over here, but if you look at previous years, it has been higher, has been lower. And you can see it wasn't even on our radar testing alone in (inaudible) trial years.

And then clicking ahead, what else we can focus on is what's right underneath it, hydroperoxides of linalool. And you can see this is pretty high over here. But clicking ahead, you can see this wasn't something that we were even testing before the 2017 to 2018 realm. So showing that there are lots of changes here and we need to

make sure that we are responding to emerging threats and concerns that are affecting our patients. Next slide.

Like I said, there are lots of new products coming on the market. I think that you look at any online website, social media site, print magazine, and you're going to see new products coming to the market and those products are going to contain new potential allergens; also, not just the new, but also the improved as well. So I always tell patients, they say, I've used the same product for so many years, you know, why all of a sudden might this be an issue? And I say it may not just be, you know, that you have new products coming in, but guess what? The formulations of these products can change and they may contain a new allergen for you. So these are areas of tremendous concern. Next slide.

And like I mentioned, it's not just the products themselves, but it's the manufacturing processes and the practices associated with those, because that can also lead to new areas of concern

that affect allergic contact dermatitis and patch testing as well. And as an aside, I'll say that one of the most impactful experiences I had when I was just out of practice was seeing an epidemic of MI in factory workers who were exposed to it not via hand soap or a personal care product, but actually as a biocide for the water that was used to harden the plastic. So these allergens can be seen in the manufacturing practices and can really lead to epidemics of allergic contact dermatitis. So ensuring that we have patch testing that reflects this is so vital. Next slide.

And I also just want to highlight our world map here to say that these products and these manufacturing practices can often be quite unique to the United States. So what works in terms of allergen approval or patch test building in other parts of the world may not be as applicable to us. We know that, like I said, there's unique patterns in terms of what we're using in the United States compared to other areas. So we need to be very sensitive to this

and to understand that this is an area we don't want to miss as we're looking at patch testing. Next slide.

So this ends with our last area of possible gaps. So I'm going to click over here, and this is going to be ensuring quality of life for our patients. So next slide.

Because, again, when we're talking about our patients, we're not talking about going from having a high burden of disease to being clear, but it's being able to sustain that clearance over a long period of time. We want to make sure that it's not just days or weeks, but months and years that they're able to stay clear and to have high quality of life. Next slide.

So what does that mean? It means that we have to ensure high-quality educational materials. And again, that's going to go back to things like access and also education of our physicians and clinicians on how they need to approach patients with allergic contact dermatitis, how to counsel with positive patch

testing. We need to make sure there's follow-up availability.

So, again, going back to ensuring that there's experts in both skin disease and patch testing that can follow up on these patients after their patch testing to ensure that they're not having difficulties following their instructions, that they're not missing anything. And also ensuring that we have the ability to expand our patch testing if we've done patch testing and patients still have persistent skin disease that's leading to concern that they have persistent allergic contact dermatitis. Because, again, that end goal is persistent improved quality of life overall. So, next slide.

So I want to end over here. I want to thank everyone for joining -- for going through the snafus of my technological difficulties over here. And I hope I've been able to frame our discussion for gaps in patch testing as we move into the next section in our Q&A. So thank you, everyone.

DR. WARSHAW: Great. Thank you so much, Alex, for that great overview and the identification of really those important gaps in patch testing.

What we're going to do now is move into our wrap-up discussion Q&A session. For this session, I'll ask if there are any presenters from not only this session, but also the earlier sessions who are still online, if you can be available. We do have two panelists specifically for this session. And I'm going to introduce them now.

First, Jim Taylor. You want to give a wave, Jim? Who is a clinical professor of dermatology at the Cleveland Clinic as well as Case Western. He's a graduate of the U.S. Capitol Page School, Indiana University and its School of Medicine, and he did two years as an occupational dermatologist at the U.S. Public Health Service with NIOSH. He has served six medical organizations in an official capacity, including vice president of both the American Academy of

Dermatology and American Dermatological Association, and is also a past president of the ACDS. He's currently an FDA special government employee and a member of the North American Contact Dermatitis Group, the Cosmetic Ingredient Review Steering Committee, and an alternative delegate to the AMA. Thank you, Jim, for joining us.

Our second distinguished panel member is Dr. Joe Fowler. Joe, if you want to give a wave.

Dr. Fowler has been a practicing dermatologist for over 40 years. He joined the North American Contact dermatitis group in 1988 and was president for 15 years of that group. He's a founding member of the ACDS as well as a past board member and president. He's patch tested, I think this number is an underestimate, but at least 20,000 patients over his career. He's currently a clinical professor of dermatology at the University of Louisville in Kentucky. And is a co-editor and editor of the seminal text on contact dermatitis, which is Fisher's Contact

Dermatitis.

So before we get to questions, I'm going to open up the discussion to our panelists, Dr. Fowler and Dr. Taylor, for your impressions or thoughts on the meeting, the presentations either this morning or this afternoon.

DR. TAYLOR: I'll go first. Are we doing a break? That was in the program?

DR. KASLOW: I think we'll just move ahead. I'm a little afraid (inaudible) --

DR. TAYLOR: That's good. Fine, perfect. I mean, I'm in favor of that.

DR. KASLOW: -- so let's just keep going.

DR. TAYLOR: Can you, can you hear me all right? I just want to make a few comments and then I -- first, I want to thank Drs. Kaslow, Rabin, and Lu from the FDA, and also Sharon, I apologize I missed your last name, very much. Incredible organization. You guys are a breath of fresh air in the conversations that we've had with you previously and then during a meeting, and

especially during the time of the government shutdown.

This last -- this Session 3 was practical implementation through industry perspective and so forth that you've just heard. And Ron asked for a candid discussion. So I'm going to start out with a candid discussion just very briefly first and just comments on some of the other things.

So we've talked about allergic contact dermatitis, but also remember we're talking about photoallergic contact dermatitis, mucosal involvement, implant reaction, systemic contact dermatitis, testing for drugs, which now are done a lot by allergists and dermatologists through patch testing. And then also I want to mention something, I'm not sure it's been mentioned. Some of the allergens that we test with are also both type 1 and type 4. And you get it. We've seen type 1 reaction especially from nickel.

The key with all of the gaps and other things that have been mentioned is we need more

allergens that are approved by the FDA, period. This is the major issue that I face and that many of us face and we have 36 approved. And it's critical I think for from a quality standpoint, from a regulatory standpoint and even, potentially, a medical-legal standpoint that we have more allergens. This is absolutely critical.

I also want to mention the -- well, in terms of we screen allergens, that's been mentioned, but also we AIM test. And the AIM test is with the supplemental allergens, but also with products that patients bring in. And this, in my estimation, is critical and has been critical in the past for identifying new allergens. Fran Storrs reported a new rubber antioxidant through testing with the rubber product itself and then actually going through a chemical analysis to identify what it is. And as (inaudible) in NIOSH and other agencies actually in academic centers have been helpful in identifying new allergens.

There are some centers that are required to use 503A compounding pharmacies, which we do,

also some government agencies, and clinics, and they've been life-saving and critical to us, especially the allergen bank pharmacy.

The other thing I just want to briefly mention is the long history of the American Academy of Dermatology and other groups involved in trying to fix this problem dating back 40-plus years through legislative action to try to change it to (inaudible) --

DR. KASLOW: Yeah, Dr. Taylor, you've frozen.

DR. TAYLOR: -- that failed by one vote in the United States Senate about five years ago. And we get (inaudible). So the -- I want to also mention, since you guys organized this meeting, I guess it went on because this was organized under PDUFA.

DR. KASLOW: Okay. Excuse me, can we just -- we need to back up --

DR. TAYLOR: I don't know what happened to the --

DR. KASLOW: -- about two minutes. I'm

sorry, we need to back up about two minutes. At least those of us here at the FDA, the conversation froze and Dr. Taylor, you're frozen. Now you're kind of moving a little bit.

DR. TAYLOR: Sorry.

DR. KASLOW: So if you could just recap what you said because it sounded like they were important points you wanted to make. We don't want to miss it.

DR. TAYLOR: Maybe I better move to the front of the house. Well, I just --

DR. KASLOW: Yeah, or you can turn your video off, Dr. Taylor, and that might help. I mean, we --

DR. TAYLOR: Okay. (Inaudible) my thing.

DR. KASLOW: Yeah.

DR. TAYLOR: Apologies.

DR. KASLOW: It's all right.

DR. TAYLOR: I can hide me. Okay. Let me go to the -- well, it's all right. I'll stay here if it works.

Well, I wanted to -- well, I mentioned the key issue is that we need more allergens. Am I still frozen or is this working better?

DR. KASLOW: Yeah, a little bit better. We hear you. We need new allergens. And you mentioned -- we heard you when you were talking about AIM testing and we heard that's -- it was after that that we lost you.

DR. TAYLOR: I'll move closer to the router. Maybe that would help. I don't know. Sorry.

Well, the point was, was that we use -- can you hear me now any better?

DR. KASLOW: Yeah, we're good.

DR. TAYLOR: Well, we need more allergens. And the bottom line is the -- I listened to the proposals that have been made. I listened to them at the European Society of Contact Dermatitis meeting in Dresden last September and that were repeated by Dr. Mahler today. And I think the harmonization with the system in Europe and Germany is critical and is

really important.

Just one comment related to that. Ron, you asked about -- or you commented on the testing subjects and I was involved with that. We were asked to retest patients in triplicate that were sensitized, and generally that worked. However, I think we balked when we were asked to retest patients that were PPD sensitive because we thought that was a hazard to the patient themselves because of the sensitivity of that.

DR. RABIN: Sure.

DR. TAYLOR: And then the -- so I guess one could test patients without a history of contact dermatitis. That might essentially indicate or identify patients that were, you know, with irritant reactions. But in that regard, you know, many of the colleagues that I worked with initially were doing predictive patch testing with animal testing and HRIPT, most of which is now gone by the by, especially in Europe, who does not allow any animal testing. But that was able -- those people were able to identify newer allergens

and problematic allergens.

The one point I'm not sure it was heard was testing with extemporaneous allergens. We often test with patient products and it's important to identify new allergens. I think that's one of the ways that we've been able to do it. Fran Storrs did this. I've tested products. And then if we get a positive reaction to the product, it's a leave-on product, then we can get the ingredients and patch test with those. And in some cases we've relied on help from the government. So NIOSH has been helpful identifying glove allergens, for instance, and the like.

So anyway, those are my comments. Thank you.

DR. WARSHAW: Thank you, Jim. Joe, I want to give you the opportunity to give any general comments or your feedback.

DR. FOWLER: Well, yeah, I echo everybody else's comment about how happy we are all to be here and how happy we are the FDA is looking at -- seeing what they can do about

expansion of patch test availability. It's certainly long been needed and very welcome.

I wonder, Erin, if we should maybe first go ahead and get some of these questions that are in the chat room, perhaps, and then --

DR. WARSHAW: Sure.

DR. FOWLER: -- maybe come back and do some summarization --

DR. WARSHAW: Sure.

DR. FOWLER: -- if we want to do that. The first one, I think that has to do with this session is, Dr. Hamann, how can one ensure an individualized compounded topical allergen meets quality control?

DR. WARSHAW: I believe Curt was having some trouble getting on, so I'm not sure if he is -- oh, there, great.

SPEAKER: He seems to be.

DR. HAMANN: I think I'm here.

DR. FOWLER: Yep.

DR. HAMANN: I think I'm here. You know, I guess if I had known that that was the

question I was going to have, we should have our pharmacist here because the pharmacist regulations and what is compounded in that space is a completely different regulatory umbrella than what we were talking about here. I know that it's up to their judgment and there's a whole different nuanced approach to how that is done. So I don't think I'm the right person to answer that. But it's -- it is a priority.

It is -- I think they do benefit from being able to compound things and it's overnighted and used the next day or within a very short period of time. But in general, it's something that's kind of outside of my particular specific regulatory understanding.

SPEAKER: There's a -- you're on mute, Erin.

DR. WARSHAW: Okay. Just to clarify for everybody that may not be very familiar, what we're discussing is the allergen bank, which is the program and the commercial availability of individualized allergens, where it's sent to -- a

physician orders it by prescription to Curt's company, that then the pharmacist makes it up for that specific patient, mails it to the physician, who then applies it in their office. So this is not a common practice, but is available to physicians that don't have the capability to keep large amount of allergens on hand, but want to occasionally patch test a patient.

DR. DeKOVEN: Well, I asked that question, you know, coming from Canada, because it seems to me a paradox that, again, there's different regulatory requirements for different products. But here we have very stringent requirements from the FDA in terms of topical allergens, of things that have been tested for years. But, of course, there isn't going to be an examination from regulatory authorities to ensure that each individual compounded allergen is going to meet the standards that it's supposed to meet. Now, it's the same thing as, say, good manufacturing practices. You have a qualified compounding pharmacist who knows what they're

doing and mixes it up. But nevertheless, there's no oversight of that. Yet there's very stringent oversight for these other allergens.

DR. FOWLER: Thank you, Joel. I'm going to move on to the next question, which is a question for Dr. Mahler. I am not sure if she is still on the line.

DR. MAHLER: I am, I am. I just tried to switch on my camera. Yeah, yeah.

DR. WARSHAW: Okay, thank you.

DR. MAHLER: Yeah, yeah.

DR. WARSHAW: Thank you. So the question is Italy's national regulatory authority, AIFA, has established a structured framework for patch test haptens, including GMP manufacturing requirements and a temporary authorization system to maintain clinical availability while full licensure is pursued. From your knowledge and experience, what lessons can be drawn from the Italian model in balancing quality oversight with timely patient access during the regulatory registration process?

DR. MAHLER: Yeah, so thank you for the question. So the Italian approach, which has been mentioned here, is a national approach in line with the two guidelines I mentioned earlier. And also in Spain, there is a national process going on in line with the two guidelines in also Germany. And the guidelines provide a long transitional period, actually of eight years, for products which have been in the market without a marketing authorization to transfer a product in a quality-controlled authorized product. And for this, at the end of this transitional period, a marketing authorization has to be submitted in Italy, in Germany, and Spain.

And so also in Germany we have still five products, five patch test products under a transitional period, which started earlier in Germany. And so what the lessons learned is that despite a very long transitional period, some manufacturers are not submitting a marketing authorization. So they are using the exemptions as long as possible and provide the substance,

even with a sticker on it, "For laboratory use only." Although it's very clearly a patch test substance which is not used in laboratory use, but on the humans, and try to use an exemption loophole as long as possible to go around marketing authorization requirements. So this is the lesson we learned.

DR. WARSHAW: Thank you. Joe, you had a question that you submitted. Maybe you want to go ahead and ask that.

DR. FOWLER: Sure. Thank you, Erin. So over the years, when I've looked at -- reading the journals back then, Contact Dermatitis and Dermatitis and still (inaudible), I guess it seemed to me that a lot of times reports on emerging allergens were much more likely to come from our colleagues in Europe than from America. And I wonder if that's due to the availability of publication because in the Journal of Contact Dermatitis it's easy to get a short report in very, very quickly compared to maybe here it's a little tougher and longer, whatever. Is it due to

that? Is it due to use differences in products or maybe is it due to the fact that patch testing and potential allergen availability has always been so much easier over there? So I just wonder what any of the presenters thought about that idea.

SPEAKER: Joe, I agree with what you said. I might -- one of the things I've thought about or pondered and I have no proof of this, but in Europe, they practice medicine differently than we do in the United States. We're dependent on clinical practice to do our job. And many physicians in Europe, especially those patch test experts have a little bit more focus on research theoretically. And so they have more time to -- and money to spend on projects where they might isolate an allergen versus in the U.S. that's quite difficult. If I want to isolate a potential allergen, who do I ask? Where do I find the funding to do that? That's -- I've thought about that as one of the reasons as well. What do you think?

DR. FOWLER: Yeah, I think (inaudible).

DR. DeKOVEN: Yeah, I would echo what, you know, Amber said. And the Europeans tend to be, for lack of a better word, sort of more collaborative in terms of, you know, research, (inaudible), you know, contact (inaudible) research group throughout Europe. And then, of course, you have the labs like Magnus Bruze's that can do this and have an interest in doing this and get some government support. They have a much more -- I think, because of their socialized medicine and the way occupational medicine is funded in Europe, they also have a greater approach to occupational diseases that picks up a lot of these allergens as well.

DR. FOWLER: Thanks. That makes sense.

DR. WARSHAW: Amber, there's a question here directed to you. Given that the global supply of patch testing, topical allergen depends on two manufacturers, what do you see as the clinical and industry risks and what steps could clinics and associations adopt to protect the cost and product availability?

DR. ATWATER: Yeah. So from my perspective and many of my colleagues, many of us who do comprehensive high-volume patch testing purchase allergens from both companies. And that is not -- the reason why is because both companies produce different allergens. There may be specific allergens we need to buy from one company versus the other. So if we were limited to one company, we would potentially lose out on availability to allergens to test our patients, to help our patients, one.

Two, I think we all hate operating in a monopoly. That would increase, theoretically increase, cost to us and, therefore, our patients in the U.S.

And how could clinic and associations protect cost and product availability? What could we do? I mean, I think I can speak for myself when I say I would hate operating in a monopoly and I would encourage us to continue to have be able to source our allergens from more than one company.

DR. WARSHAW: Couldn't agree more. This is another question for Curt from John Elliott (phonetic) in Canada. I'll summarize it here, but it sounds like there was some discussion that it costs approximately $120,000 in the U.S. to complete the testing required by PEI to get a new batch of sesquiterpene lactone mix syringes approved. And the question is, is that a typical cost for each new batch of syringes and, if so, what is the average cost per syringe and are these costs sustainable at the current market prices?

DR. HAMANN: Thank you, Erin. I wasn't a part of the specific conversation, but my interpretation of what I'm hearing and seeing here would be that this is not a fee for the batch. This was the development cost over several years of developing the -- and validating the analytical method that is then used as the stability indicating method for batch release. So once that has been validated and it has been approved by PEI, then that becomes a standard practice that no longer has that recurring significant investment.

This would be an investment that's just what is necessary to develop and deploy the method in a -- in an acceptable way for PEI. And I don't know whether that number is super accurate, but it wouldn't surprise me.

DR. WARSHAW: Thank goodness that's not the cost per batch.

DR. HAMANN: Oh, it is definitely not. And there are -- you know, many of these allergens, the development of the method is quite simple and not costly at all. Ironically, though, those are the ones that were figured out first, so they pushed all the difficult ones until I got on board. So the last, you know, 10 years, we've been working on all the ones that are really, really complicated and those do tend to be more expensive.

So it's -- you know, when you try to do something for a composite mix, super complicated. If you really want to have something that is a release criteria for a batch that's going to ensure that every time you buy it, it's going to

represent what you think it's supposed to each time, the method's really complicated. Really, really complicated. And, you know, that's why it's impossible for the hydroperoxides of limonene and linalool. There's so much stuff in there, I don't even know what it is, don't even know where to start. And that's why it gets complicated and why the regulators are giving us pressure. They want answers.

DR. WARSHAW: Seems like for these botanical extracts that vary in composition and are so complicated that there needs to be a different set of guidelines than something like a metal salt, which is relatively simple.

DR. HAMANN: Yeah, I think that they are actually doing that. I mean, they could be coming back to us and saying, what are these other 50 things that you've not identified that's in this mix? That they have compromised on what they would typically do for an API, and I'm grateful for that. But they still want to know what are the significant peaks that we believe are the

allergenic ingredients that are critical for this to work? And they give us some grace at times with some of the things that they otherwise, from a regulatory point of view, don't have to.

SPEAKER: I think Dr. Mahler commented on that earlier. I wonder if she has any other comments.

DR. MAHLER: So I -- is my camera working? Yeah. Yeah. So indeed we distinguish between a metal salt and complex extract from nature, actually. So -- but at least, as Curt said earlier, it is important to have the relevant components in there. Yeah. So this is the minimum requirement. But so we are quite compromising also from the batch-to-batch consistency that there might be a small difference between because it's a natural active substance and there have to be some flexibilities.

DR. TAYLOR: So I'd like to move the conversation a little bit towards -- well, perhaps I need to recap, you know. First, you know, being here at FDA, that what we hear, you know, we've

heard loud and clear that the American market needs more patches. We've heard loud and clear that, you know, you appreciate what the European market, you know, has done to set -- to stop this problem over there and, you know, whether or not we could use that as a model here. And you know, my answer off the cuff is we could use -- you know, to some degree the answer is yes, to some degree the answer is not so much. And because there's some devil in the details because, you know, we have our laws and regulations and they have theirs, and that's going to require some thinking on our part and some conversations internally and with colleagues and, you know, we're prepared to do that.

What I am wanting to hear are what -- first of all, I was hoping to hear from Curt a little bit more because, you know, I see these patches and I see, you know, even with TRUE Tests, I see this is at this percentage and this is this particular salt at this percentage. And I don't get a sense of how you arrived there. And I'd

like, you know, how you arrived, you know, what sort of tests that you did to ensure that you were at a maximum concentration with a minimum amount of irritation. Which to me is, you know, from what I've been hearing, and I'm obviously the very least experienced with this, you know, clinically, I have no experience, but from what I've been hearing is, you know, a first, you know, requisite, if you will, of these patches to get the best concentration you can get, to cause the minimum amount of irritation. And then, you know, so I kind of want to know that.

DR. HAMANN: So I can answer.

DR. TAYLOR: Yeah, so perhaps you could just address that. And then I have a couple of other questions and comments where I sort of need the conversation to go for us.

DR. HAMANN: Yeah, that's good. The phase 2 clinical trials that have been performed for all 35 of the preparations that are approved all did a dose response series.

DR. TAYLOR: Okay.

DR. HAMANN: And it had -- it either had four doses at a log difference of each or five.

DR. TAYLOR: Okay.

DR. HAMANN: And it was that data that was used for us to select which was the proper dose to go forward into the phase 3 clinical trial. So I believe that the disciplines for TRUE Test were very, very significant.

And the way that we decided what was going to be the middle dose that we would then bracket with the log dose above and below for most of the metals and many of these core allergens, it's because there were dose response series done in some of these centers of excellence that you've already heard about. Magnus Bruze's group, for all the metals, they have done dose response series of all of them with different salts, with different excipients. And, therefore, we have in the literature a really, really good lead. So that when we were going forward with our phase 2 clinical trial, we chose the salt 1 or 2 and that dose based on what was already in the literature

for what had been learned with dose response studies that had done before.

So I think that for the core allergens, there's a lot of data, Ron, that is really, really good.

DR. RABIN: Okay. But what about the other 150 or 200 allergens that, you know, or 300 allergens that have just, you know, been licensed, you know, authorized in Europe? Are we confident of those?

DR. HAMANN: I think it's a great question. And I think one of the things that's ironic about this is if you look in the literature and you see what's published, you'll see, well, the Italians, they wanted it at 1 percent, and then the Germans, they wanted it in 0.05 percent, and then Magnus wanted it 5 percent. And so it's almost like the literature's already got the dose response series done with different groups that have said, no, chemo technique or smart practice make this different dose for us because we think theirs is too low. And so there's a lot of data

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DR. RABIN: Okay.

DR. HAMANN: -- even for these 200 that you think there isn't much data. There's a lot of data. And that's where I think then when you go back and do the well-established use justification with what PEI and IFA are doing, you bring all that literature together. These guys were using this percentage, they were using that percentage. And that's where we then land on what we think we should go forward with. And then if it's still unclear, then I think we've said, then go back and do some sort of a nested phase 2/phase 3 small clinical trial. Just make sure we get it right. I think there's a ton more data than you think.

DR. TAYLOR: Okay. Well, that's good. And what to Dr. Belsito's comments. Now, I think we heard from Jeff this morning that he wasn't concerned about patch testing kids, you know, neosensitizing them is I believe what I heard. But that is a -- how much of that is a concern amongst those of you who do this?

SPEAKER: I think --

DR. TAYLOR: Can there be too much?

SPEAKER: The FDA decided that that was a concern and that's when they came back to us and said, you need to do a clinical trial in children for your licensed product and be PRIA compliant. And so we went and did a children's study with the existing TRUE Test 35 allergens. And there was -- there were no indications there was any problem, even with PPD, which you heard from Jeff, might be a problem. The PPD on TRUE Test --

SPEAKER: Might be a problem with neosensitization is what you're saying.

SPEAKER: So clinically when we --

SPEAKER: Go ahead.

SPEAKER: Clinically, when we perform patch testing, we express the risks to our patients as we would for any procedure that we do in the clinic. And one of the things that we mentioned to our patient is that there's risk of sensitization with patch testing in theory. And I think most of us who do patch testing can tell you

that it does happen. It is rare. It is exceedingly rare. And the way that we find out about it is the patient comes back three, four, five weeks later and has a new positive.

SPEAKER: Right.

SPEAKER: I can say I've seen it once or twice over, however -- since 2008, however long that is. So it's exceedingly rare. It can happen, we know that. I think Don's point is that also in the literature, just like there is our reports of the recommended test concentration dose, there's also reports of how much is too much? Are we causing sensitization? What's the irritancy potential? And there's tables on, so many allergens in the literature. And, and that's where Curt gets his numbers from, where to start?

SPEAKER: Okay. Okay. Thank you.

SPEAKER: So then the next question that I have --

DR. DeKOVEN: That was my point. That was my point, Ron. You said, you know, an allergen at maximum concentration, and that is not

irritating, but sometimes that allergen could be inducing sensitization. And so that's also a critical factor in commercializing an allergen.

DR RABIN: Okay.

DR TAYLOR: Can I mention one other thing?

DR RABIN: Please.

DR TAYLOR: Sorry. It's related to this. The most pediatric patch test recommendations suggest using plastic chambers rather than aluminum chambers because of the prevalence of aluminum allergy, especially in kids that Jeff mentioned, o.

DR. RABIN: Okay. That's useful information. Thank you. Okay. So then a next question is, you know, with regard to, you know, you've got, you know, you want 100 allergens or 150 allergens approved, you know, because you really need this expanded list. And we've heard it. We hear it. And this is a question for you, Vera, as well. I mean, you know, we're looking at these numbers, we're looking at these RIs and

these PR numbers, and we're not, you know, we're not -- obviously, we don't deal with it in real time, you know, so we just look at these numbers.

And for some time, for some of these allergens, when I look at these numbers, I feel like I'm in a, you know, a high school class where everybody -- where like half the class is getting a D, so a B minus is an A. And, you know, we're all happy with that. And that, you know, in a sense that while Europe -- you know, while you and PEI did a great service to the specialty and to the patients by, you know, granting authorization to a large list of allergens are, you know, are you where you want to be with quality of some of these patches in such a way that if we approach it, you know, based on your model, do we have an opportunity to say, you know, there's a particular set here that we ought to get, that we could make better? Or even there's a particular set here where the numbers are really so not good that something isn't better than nothing, right? Right. You know, because I'm looking at these

numbers and that's what I'm thinking.

And I want to hear what you think about that, Vera, and I want to hear what the expert clinicians think about that.

DR. MAHLER: So thank you for this really, really relevant question. So -- but it is a fact that -- so the active substances are chemicals. And besides their allergenic properties and capacities, they have less or more all also some irritancy that is just a matter of fact for these chemicals. And therefore, we have to live with the fact that there is some irritancy.

Of course, a patch test allergen with a reaction index of minus one, there we really have to ask the question, is it an allergen or is it just an irritant? However, this is due to the specific properties of these haptens. They are also irritants. And therefore, we would not reject an marketing authorization application because of these bothersome numbers. But we think it is important to make it clear in the SMPC that

this is not an ideal patch test reaction and not every reaction you see is an allergic reaction. But there is irritancy to be expected with this specific patch test substance. However, these substances reflect also the exposure in the environment.

A rubber accelerator, for example, we heard of one of the testimonials of the diphenylguanidine. And so this has a higher irritancy also in reality, in the true exposure. And so I think this is something we have to live with it. And even if we manage somehow, through a manufacturing process to get these much better, they would in some cases maybe not reflect anymore the true exposure in the environment.

But of course, I agree with Curt. It's feasible to do some dilution testing to see what is the best constellation between the two positives and irritancy. So that is feasible, but we won't get away from some irritancy in these group of actives substances.

DR. RABIN: Sure. Okay.

DR. FOWLER: Ron, I hate to complicate your life here more, but one thing to remember is when these patch tests are being called irritant or positive, that's a subjective observation by, you know, some local expert, hopefully an expert. And so maybe some of those that were called irritancy were really positive. And, you know, you have to go back and talk about relevance and finding out all that stuff that we have to do clinically, whether that reaction turned out to be relevant. So --

DR. RABIN: Yes.

SPEAKER: -- you know, that number alone, you know, doesn't really necessarily hold a whole ton of water. I mean, it's okay, but it's not perfect.

DR. RABIN: Okay.

DR. FLAMM: Yeah. From that standpoint, I think. What's really important to understand when we're looking at this, at least from our -- from a clinical standpoint, it's that we're looking at the pooled data. So really what's

important is that we've all seen relevant reactions to these allergens and it's made a significant difference for these patients and it's important for us to have them. But like you said, it does go into the area of education. If this is something that has a higher irritancy rate, it means that we need to make sure that we have patch test experts who are skilled in understanding the difference and understanding which patch test allergens have a higher likelihood of causing irritancy and being able to have appropriate clinical suspicion around it.

DR. RABIN: Okay.

SPEAKER: Yeah.

DR. DeKOVEN: And I would just like to say --

DR. RABIN: Yeah, (inaudible).

DR. DeKOVEN: You know, cost-benefit, you know --

SPEAKER: (Inaudible) patients give him a (inaudible).

SPEAKER: Yeah. I'm just building off

of what Alex said. I think perfect might be the enemy of the good here. And I would contest that. You know, and I really applaud, you know, the amazing diligent work that Curt and his team do to really try to get it right. But I think, you know, if, you know, getting in the right range is okay, and I think a lot of the patients, you know, whether it's a two fold dilution or a four-fold dilution, you're probably -- you know, using the literature and using the knowledge of related compounds, I don't necessarily think for most of these it has to be perfect.

And you know, there's -- it's not all about the allergen. Right? I mean, there's so much variability. It does come down to education, it does come down to when you read the patch. Right? So if you read it at 48 hours, you're going to miss; 72, you're going to capture more; 96, you're going to capture more.

SPEAKER: Yes.

SPEAKER: The other analogy I want to make is if you, you know, you think about topical

medications and drugs, right? They're approved. They go through testing. We have no idea how patients are putting these things on their skin. Some could be putting a thick coating on, some could be cutting a thin coating. Sometimes they occlude it. The same variability exists in the patch testing world. I mean, you know, we try to put the same ribbon on, but that's not standardized. So I really caution us about perfect is the enemy of the good.

DR. RABIN: All right. Message was received. Okay.

SPEAKER: And Ron, I want to comment on one other thing you said earlier, and you're right about it's -- something is not always better than nothing. But I would say it almost always is. Because let's -- so let's say we have a positive --

SPEAKER: Okay. All right.

SPEAKER: -- reaction to something --

SPEAKER: Getting a lot of pushback on that, I hear it. Okay.

SPEAKER: So let's say we have a positive reaction that we call positive. We tell the patient they're allergic to X, Y, and Z, and the patient goes out and avoids X, Y, and Z and doesn't get better. Or the patient is getting better and then goes out and exposes him or herself to X, Y, and Z and doesn't have a problem. Okay. Then, you know, we haven't really permanently caused any harm to that patient. We just kind of made it inconvenient for them for a while.

And let's say we told him it was negative, the test was negative, which is probably worse, I think. But then that patient still keeps having problems with it. Well, they're probably going to come back to somebody and, hopefully, maybe the next time we patch test them, for some reason this bioassay turns positive. So, again, it's not like we have permanently -- you know, it's not like we caused to cause them to have leukemia, you know, or something from what we did show them.

SPEAKER: Yeah, no, I -- I mean, a false positive, somebody could, you know, leave their job, you know, by -- but I'm not as worried about the false positives as I am, I guess, the false negatives, some of these really low numbers that we saw.

SPEAKER: Yeah.

SPEAKER: But, you know, I hear the point. This isn't a CBC. You're clinicians, you're, you know, you're interpreting data, you know, in the context of patient and history and a of -- lot of other things. This is an (inaudible), so, I get that. I hear that.

RABIN: Be very interesting, I'm just thinking this is totally applicable. It would be very fascinating to see whether or not you could train AI to give you consistency in patch test reading that maybe humans couldn't do. It'd be kind of cool. Curt wants nothing to do with that.

There are people actually into that right now.

SPEAKER: I'm sure somebody's thought of

that. I'm sure somebody's thought of that. That's a digression.

SPEAKER: You mentioned about the possibility of false positives. If you're only patch testing to 36 allergens, you have a much greater chance of having, you know, false negatives. Right?

SPEAKER: Missing. Missing diagnosis. We get there. Believe me, we have heard that message. We got it.

DR. WARSHAW: I think I just want to clarify a point because we've been throwing around the term "irritant reactions," "irritant patch test reactions." And just for the non-clinicians in the room, non-patch testers, that does not mean it's an asymptomatic reaction to the patient. They're totally unaware. It's just we're seeing macular erythema on their back. It's not a side effect of the patch testing. So just want to clarify that, that it's just macular erythema. It's not asymptomatic.

I think of it, not to beat a dead horse,

but I almost think of this as analogous to, you know, ANA testing. You know, we get a lot of positive. But it takes a clinician to explain to the patient that, you know, these borderline titers are not often clinically relevant. And we do the same with these borderline patch tests that we really want to see those strong vesicular reactions, you know, the high titer, if that's --

SPEAKER: Okay. I'm just asking my colleagues in the room. Yeah. There -- I think that we're -- obviously, if you wish to -- you know, if there are other things that you wish to share with us, we're all ears. But I -- our sort of questions have been answered. So it sounds --

DR. WARSHAW: Yeah. I was just going to open it up to the group. Does anyone have any last comments?

SPEAKER: Just a question for Ron regarding PDUFA. The -- you had the open meeting on -- I think it was in June. Has there -- a formula been --

RABIN: So that's above our pay grade.

Okay. We don't make those decisions. We've been sort of in the other room hearing them and, you know, people -- you know, we've been part of the discussion at a lower level, but I don't, you know -- and, you know, I have some impressions about, you know, where things are going to go, but it's not really appropriate for me to share with you my envelope thoughts about that. That's done at the commissioner's level, at (inaudible) level. We -- I think we've certainly heard from you that, you know, you agree that these products should be exempt, you know, should be PDUFA exempt. And if we're given the opportunity to share that with the people who make these decisions, we will share that with people who make these decisions.

SPEAKER: Thanks.

SPEAKER: I have one additional question, Ron. I was just -- and you may actually be going into this next, but what do you see as your next steps here and how can we help provide, you know, good (inaudible).

DR. RABIN: Sure. So here's how, you

know, we see things going. Okay. I mean, the first thing that we need to do, which it sounds rather bureaucratic, but it's actually important. It's sort of, personally, it's part of my process is that, you know, we need to go over the transcripts and the recordings and put together, you know, a proceedings document that will be published. And obviously, I will need your help with that. You, the speakers who have been here, you know, to proofread, make sure that what I wrote is correct and complete. And that's important for us because basically that helps me really think through the process and pay attention to details that, you know, remember from earlier this morning or may have just slipped by me.

And I think that once we have that document that we internally are comfortable with, you know, we can take that document and we can say, okay, now, you know, we comprehensively understand the situation. What do we want to do with it? And I think that what we agreed in here is what we want to do with it is we'll probably

initiate some conversations with our European colleagues to talk to them about their model. And we will, also, of course, initiate some conversations with -- I mean, Dr. Kaslow is upper management, but even, you know, further up to understand what our latitude is towards, you know, towards applying some sort of European model.

For example, we don't have a well-established use program here. You know, that is inked into the, you know, the European, the EMA, but we don't have that here. And, you know, what does that mean? Does it mean that there's another way that we can do things or not? You know, we're not sure. And even if we had an idea today, it's not something I would share (phonetic) off the cuff.

I think that sometimes then what, you know, eventually is we make a decision. You know, there are various ways we communicate the decision, you know, through a Federal Register Notice, you know, through a guidance document, through some sort of an official document that

ensures that we're communicating it to all the stakeholders at once and not favoring one stakeholder over the other.

I think that I can say with confidence that this wasn't just a talking session. We had this workshop because we understood that it was time to take some action, that it was time to do something, and we wanted and we needed to hear from the experts about what to do.

I guess I'm sort of going in my closing remarks here as well. So first of all, did that answer your question? Are you -- does that -- everybody's kind of nodding.

SPEAKER: That's very helpful. Just to, like you said, this is a new territory for all of us. So we want to make sure we're being --

DR. RABIN: Sure.

SPEAKER: -- (inaudible) through this process.

DR. RABIN: And I'm going to promise you that it's not -- that no matter how fast we do it, it's not going to be as fast as you hope it is,

because that's just life, life in a government agency. Because the more, you know, the more you're changing policy, the more people's -- the more eyes are going to be on the document. Okay.

I do want to say a few things. First of all, I do want to thank Dr. Mahler for staying up so late and I want to thank Dr. Chen and anyone else on the West Coast for getting up so early. I really appreciate all that everybody has done.

There's one person that wasn't recognized early on and acknowledged, and that is my colleague and my boss for over 21 years, Jay Slater, who put this thing together really initially, and then it got called with the change administrations and other things. But, you know, really, it -- I did the easy part. He found you all, he had the initial conversations, and it was kind of easy to put together. And I really appreciate that.

And I also, again, want to thank Lonnie and Stacey and people who have really helped us put this together because, you know, a few

technical glitches here and there, but I think we've all -- it's worked out fairly well.

So that's all I have to say today. And if anyone else has any other comments, I think we can call it a day. And we'll call it a day. Thank you all very much.

GROUP: Thank you.

(Whereupon, at 3:56 p.m., the PROCEEDINGS were adjourned.)

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CERTIFICATE OF NOTARY PUBLIC

DISTRICT OF COLUMBIA

I, Gary Euell, notary public in and for the District of Columbia, do hereby certify that the forgoing PROCEEDING was duly recorded and thereafter reduced to print under my direction; that the witnesses were sworn to tell the truth under penalty of perjury; that said transcript is a true record of the testimony given by witnesses; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this proceeding was called; and, furthermore, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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