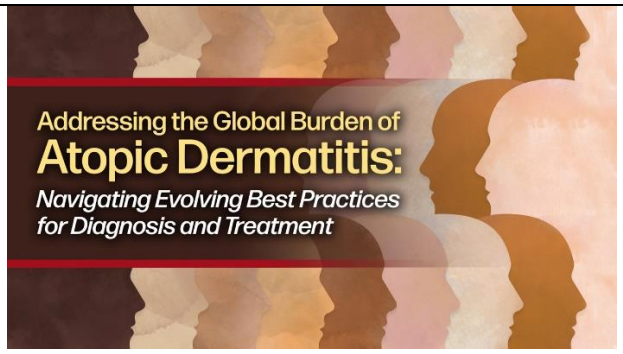
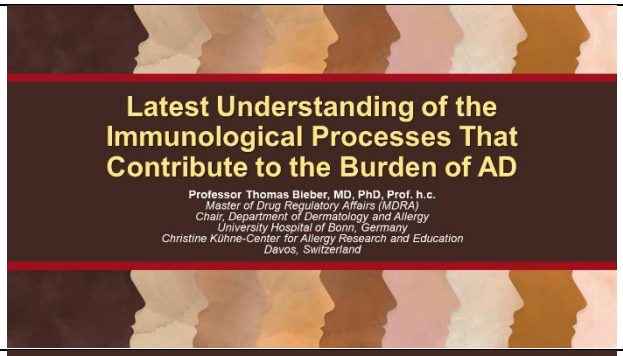
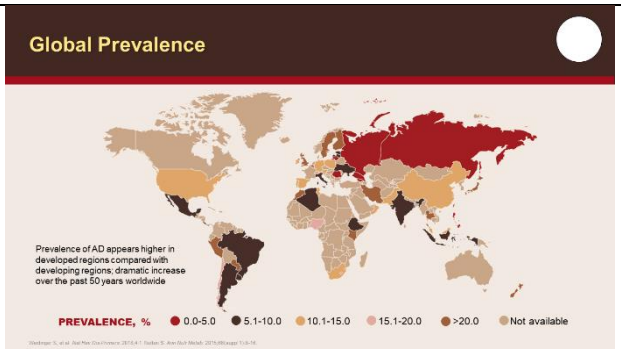
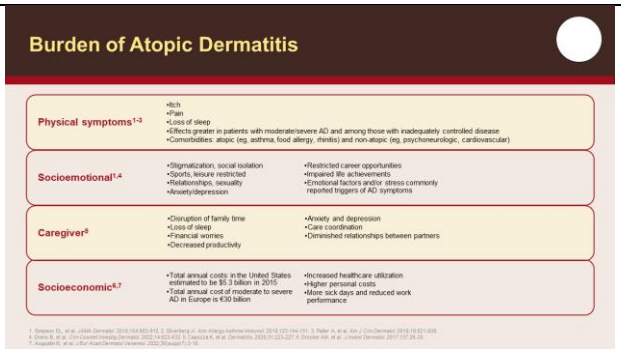
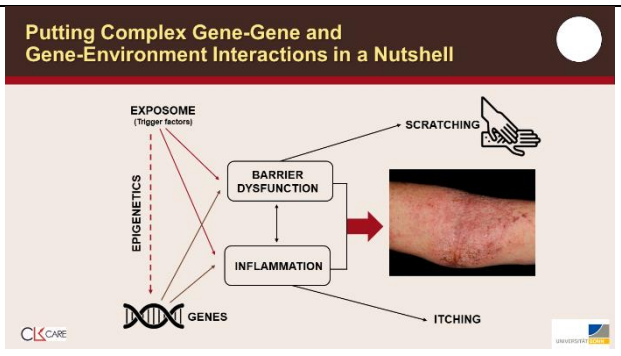
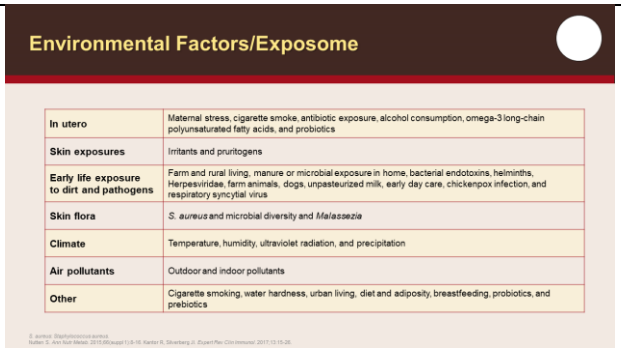
Addressing the Global Burden of Atopic Dermatitis: Navigating Evolving Best Practices for Diagnosis and Treatment

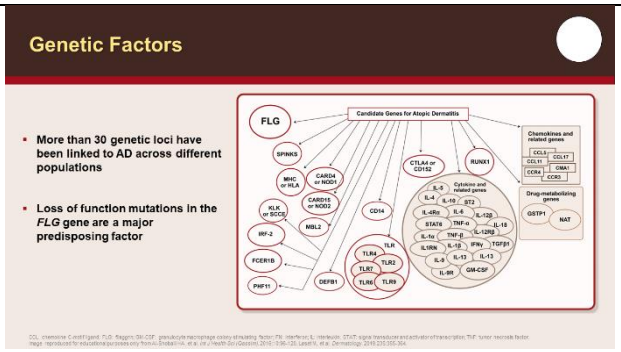
Latest Understanding of the Immunological Processes That Contribute to the Burden of AD

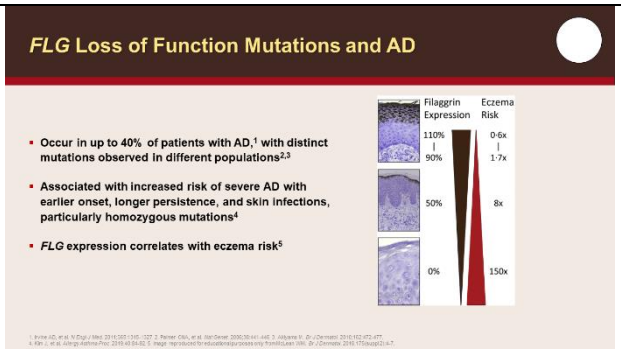
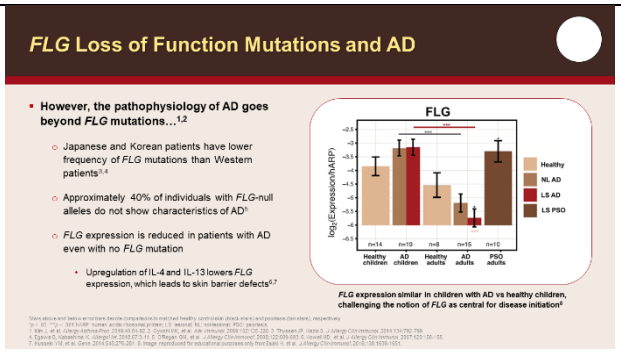
1		Hello, my name is Thomas Bieber, I'm a dermatologist and allergist at the University of Bonn in Germany, and I welcome you to this series of presentations, Addressing the Global Burden of Atopic Dermatitis.
2		In this presentation, I will go through the different aspects of atopic dermatitis with relationship to the immunological processes that are contributing to the disorder.
3		So as you certainly know, this disorder is the most common chronic inflammatory skin disorder in dermatology, of course, besides psoriasis. And it's also known as eczema or atopic eczema. It's the most frequent one that affects, I would say, a quarter of the children or the newborns and drops to 3% to 10% of the adult population, and this is due, mainly, because there is this very strange phenomenon of spontaneous remission that occurs in childhood between the ages of, let's say, 5 and 10 years. The disease itself is characterized by quite substantial pruritus with recurrent lesions, flares, and, most importantly I think for the practice, is that we have to understand that this disorder is really a highly heterogeneous

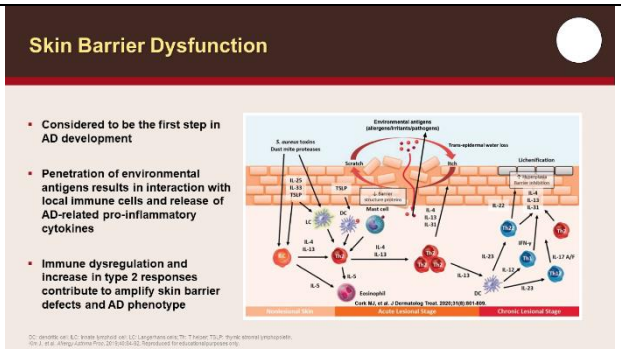
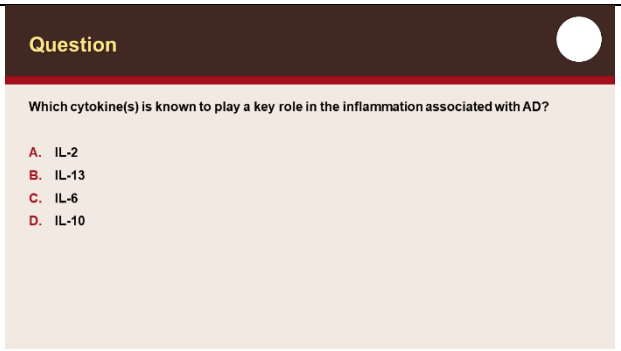
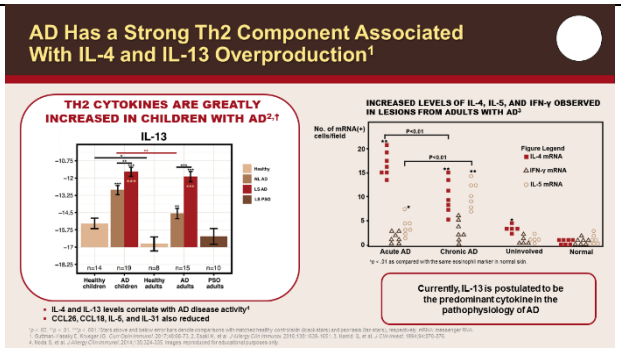
		clinical phenotype. So, most of the age of onset typically is localized in the early childhood between 3 months and 6 months of age, but it could also be appearing afterwards, between 2 years and 6 years. We also have some patients starting the disorder during adolescence and, overall, 20% of the patients start the disease in adulthood.
4		With regard to the global prevalence, we have a number of data and studies available. For example, the ISAAC study has nicely analyzed the incidence and the prevalence of the disease among different countries. And you see here that the prevalence seems to be low, in particular, in Russia, while it is quite substantial in other countries, particularly in Western countries. And that's the situation that currently has been analyzed, and we see definitely a dramatic increase over the last, I would say, 40 to 50 years.
5		So, the disease itself is well known to induce quite a substantial burden on these patients, particularly due to the itch sensation, which induces loss of sleep, and has quite a number of comorbidities, so all the atopic, all other atopic

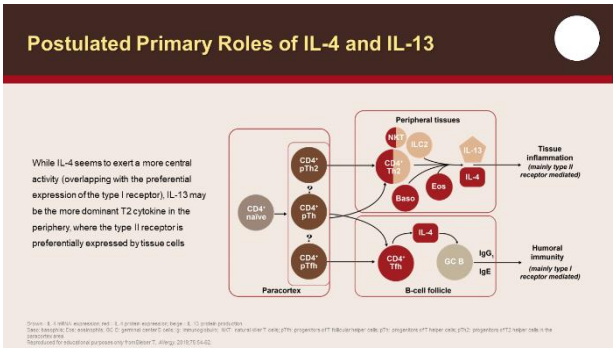
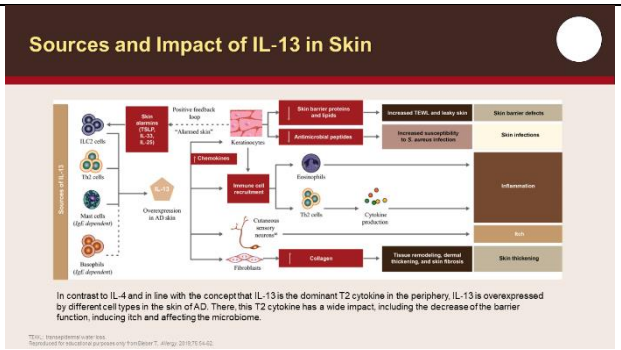
		disorders, like asthma, food allergy, and rhinitis, as well as non-atopic comorbidities, like psychoneurological and cardiovascular disorder, can appear in the course of the atopic dermatitis. We have a number of socio-emotional aspects, particularly the stigmatization of these patients, particularly when some areas like the face and the hands are particularly involved. For the caregivers, atopic dermatitis is sometimes a huge issue, for the kids in the family. And this leads not seldomly to a disruption of the family time and to main issues related to the financial worries that the patients or the caregivers have in the context of the management of this disorder, and this is reflected by the socioeconomic aspects. So just to give you some numbers, the total annual cost of moderate-to-severe atopic dermatitis in Europe is estimated to be 30 billion Euros.
6		So, in a nutshell, when I'm explaining the disorder to my patients, that's the typical picture that I'm showing. I'm trying to educate the patients in a very simple way, showing them where the issues are. And the issues are definitely first in the genes that are encoding, on one hand, the barrier dysfunction, on the

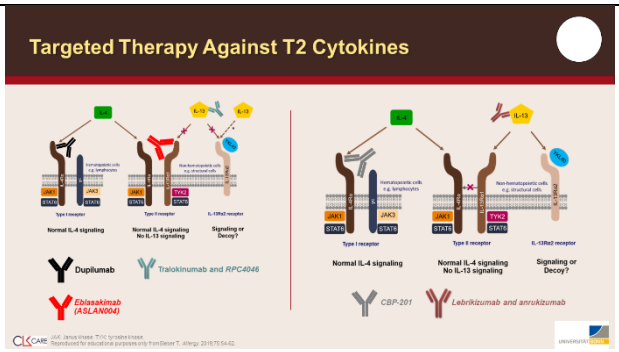
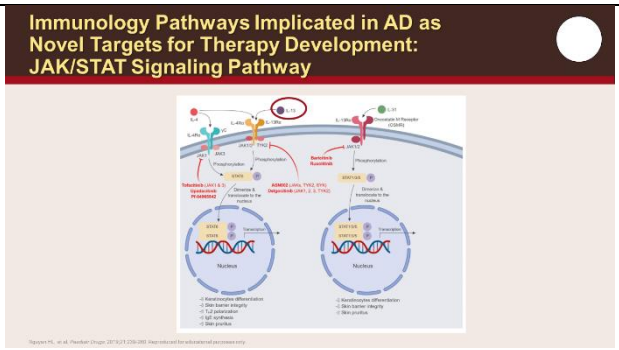
		other hand, are responsible also for a number of immunologically relevant structures that are involved in the induction of the inflammation. On the other hand, we have the exposome or the environmental trigger factors that may play a role and that also are able to interact with the immune systems through the barrier dysfunction, but also in terms of epigenetic regulation, we think that there is something here that could be of interest in research for the next decades of work. In terms of symptoms, the scratching is very important, and this is the main symptom of most of these patients and this scratching, of course, is the result of this intense itching sensation that most of these patients have and that is triggered by the inflammatory reaction.
7		So in terms of environmental factors or exposome, we know that there are a number of different kinds of factors playing a role, particularly the skin exposure with irritants and pruritogens in the very early phase of the disorder. The microbiome issue, which is heavily debated currently — which is very hyped, I would say — so the skin flora and the composition, the real role of

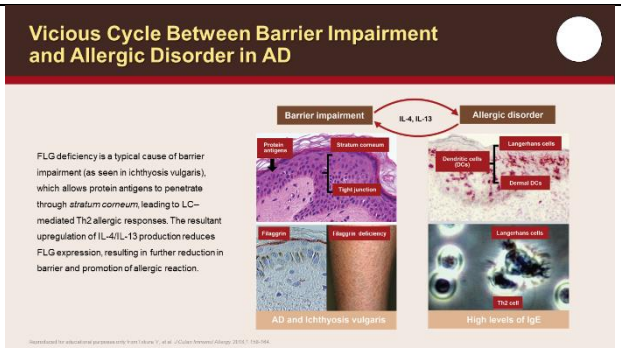
		Staphylococcus aureus seems to be prominent, I think prominently more in the pediatric population than in adults. Of course, air pollutants may play a role as provocation factors. And last but not least, cigarette smoking is well known as a provocation factor and an important environmental factor in the context of many epidemiological studies.
8		So, with regard to the genetic factors, I think as I mentioned before, we have two classes of genes that are relevant here. The first class is those genes relevant for the issue of the barrier function, and this is shown on the left side of the slide. Particularly filaggrin, which is the most prominent one which is detected, I would say in something like 50% of the patients overall worldwide. On the other hand, we also know candidate genes related to a number of structures, including the Toll-like receptors, but also the cytokines, proinflammatory cytokines, and other chemokines that are relevant for our understanding of the immunology of this disorder.

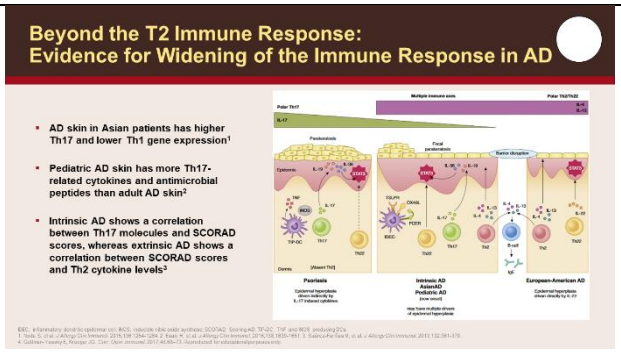
9		And when it comes to the filaggrin mutation, we know that this is extremely important because, as I mentioned, it occurs in the substantial part of the patients, it's associated with an increased risk for severe AD. But not only that, it also is highly associated with the persistence of the disorder, skin infections, and also I think it's well known that these patients have a high risk to develop food allergy and some other comorbidities.
10		So, the filaggrin mutation is one thing, but we know that the pathophysiology of AD goes beyond that filaggrin mutation. We have a number of different kinds of gene variants and mutations that are known to be quite different depending on the different kinds of populations that we consider and whether we consider also patients in adulthood or in childhood. So, the filaggrin expression is similar in children with AD with healthy children, but challenging the notion of the filaggrin mutation as a central part of the disease initiation.

11		So, there are a number of other genes that may be responsible for this, and this is a little bit depicted here. The skin barrier dysfunction, of course, is of importance because it allows the penetration of a number of environmental allergens and irritants. And all the kinds of pathogens that then are able to go through the disrupted barrier function and to interact directly with the local immune system.
12		So one of the first questions is: Which cytokine is known to play a key role in the inflammation associated with atopic dermatitis? So, you have the choice between four here: IL-2, IL-13, IL-6, and IL-10. And, of course, the answer is IL-13.
13		You will ask why is IL-13 so important and not IL-4? First, I think we have good evidence currently that IL-13 is probably the major driving force of inflammation in atopic dermatitis, because you can measure these cytokines in high levels, not only in the skin, but also in the circulation of the patients suffering from this particular disorder. But, of course, you can measure a number of other cytokines in the skin, as well as a biomarker in the periphery.

14		However, most probably IL-4 is not playing that same role in the periphery. In contrast, IL-4 is known to be a cytokine that is mainly expressed in the central part of the immune system and most probably related particularly to other mechanisms, like the humoral immunity, and IL-4 is well known to be one of the most important cytokines in the regulation of the IgE synthesis, and you know that IgE is a typical hallmark in the vast majority of patients suffering from atopic dermatitis.
15		On the other hand, as I mentioned, IL-13 is the most important driving force in terms of cytokines in the skin itself. You can measure a huge amount of this cytokine in the tissue, particularly in the lesional skin, but also in the nonlesional skin and the biological activity of those cytokines is just depicted here. You see here clearly that IL-13 is not only inducing inflammation, but has a deep impact on the barrier function, it has an impact on the microbiome, it is also able to directly induce itching sensation, and indirectly, by inducing the collagen synthesis, it somehow also contributes to the dermal fibrosis that is seen in most of the patients. So now the question is: How

		can we, by kind of strategic pharmacological approach, try to have an impact, particularly on IL-13?
16		And now currently, we are very happy to have at least two biologics which are targeting IL-4 and IL-13 either by binding at the receptor like dupilumab or binding at the free cytokine like tralokinumab. And this picture also shows you clearly that we have a number of other molecules currently in the pipeline, particularly lebrikizumab, which is now in the final phases of the approval, and some others like cendakimab or RPC4046, which are also in the pipeline, as well as eblasakimab. So, you see here currently the number of molecules or biologics that are in the pipeline are interesting and I think we are all keen to see all these products be available in the next time for our patients.
17		Beside these biologics that have to be applied by injection, of course, we have now the new generation of the so-called JAK kinase inhibitors. These inhibitors, in fact, are acting directly on the signal transduction machinery, which is involved in the biological activity, particularly of IL-4 and IL-13, but also of other cytokines, like IL-31, which is mainly

		responsible for the itching sensation. And these pictures just show you the different kinds of kinases involved here: JAK1, JAK2, JAK3, and TYK2. For all these different kinds of JAK kinases, we now have different kinds of products available, the so-called JAK kinase inhibitors, for example, baricitinib, which is blocking JAK1 and JAK2, or upadacitinib and abrocitinib that are binding mainly or selectively to JAK1. And of course, a number of other molecules which are less selective, so-called pan-JAK kinase inhibitors, like delgocitinib that are also acting efficiently in this disorder.
18		So, one of the biggest issues in that particular disorder is this vicious cycle between the barrier impairment and the allergic disorder in atopic dermatitis, because as I already mentioned, we know that the barrier impairment allows the penetration of quite substantial number of substances in the skin, and then by this they have direct contact to the local antigen-presenting cells, particularly the Langerhans cells in the epidermis and other cells, like dermal dendritic cells. And in combination to, particularly the filaggrin mutation and the local inflammatory reaction, this

		leads in fact, at the end, to the activation of or to the emergence of hygiene-mediated sensitization that particularly emerges from that interaction in the skin of the allergens to the antigen-presenting cells, and then the antigen presentation leading, finally, to a specific adaptive immune response, including the generation of allergen-specific IgE.
19		And this, as already mentioned, this highlights the role of the so-called T2 immune response in the context of atopic dermatitis. But as mentioned here, we now know that this T2 response is not the only one that is effective. We know that there are a number of other immune responses like Th22, Th17, and Th1 that are also relevant, particularly in the Asian population where Th17-related cytokines have been measured in high amounts in lesional skin of atopic dermatitis. In the so-called atopic dermatitis of the intrinsic form, there may also be some correlation with the Th17 pathway, but this is still unclear and needs further confirmation. I hope I was able to summarize here, somehow, the current knowledge in the immunology of atopic dermatitis and to highlight a little bit the issue of the core

		T2 immune response that is followed by the widening of the immune response in this atopic dermatitis issue. This, in fact, somehow resembles to a kind of immunological march, and that immunological march is in fact offering a number of targets for pharmacological interventions and for the development of new drugs.
20		Thank you very much for your attention.