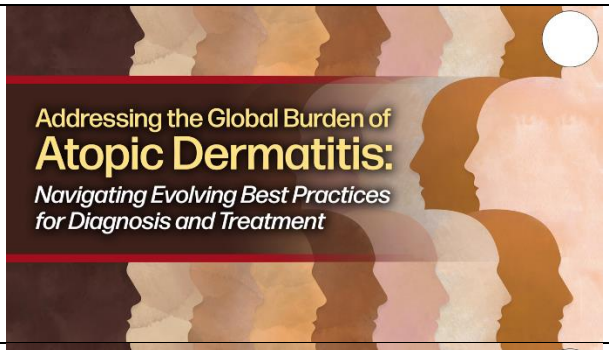
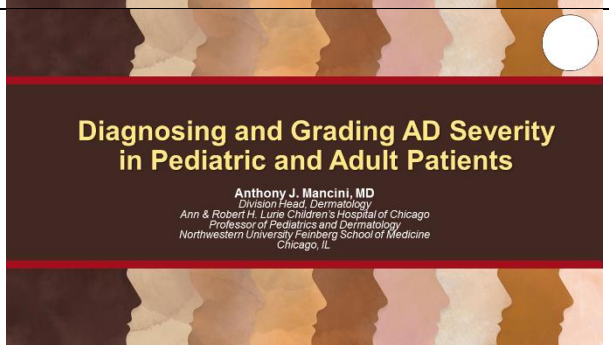
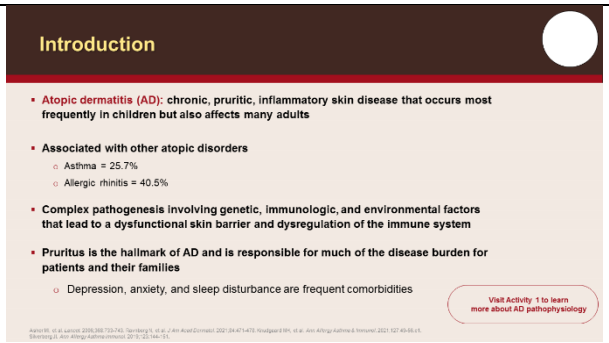
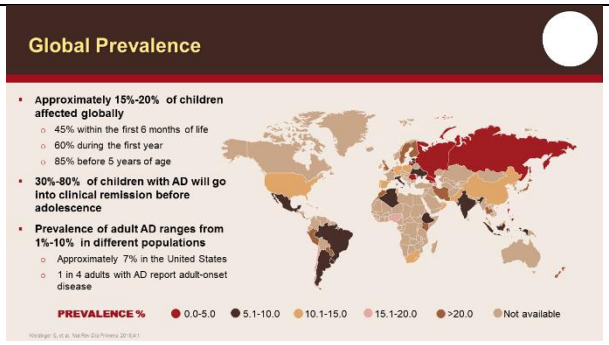
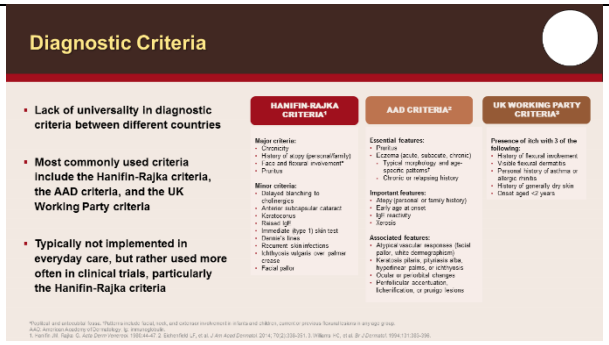
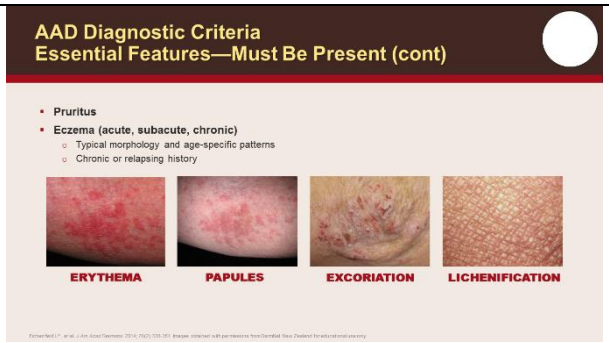
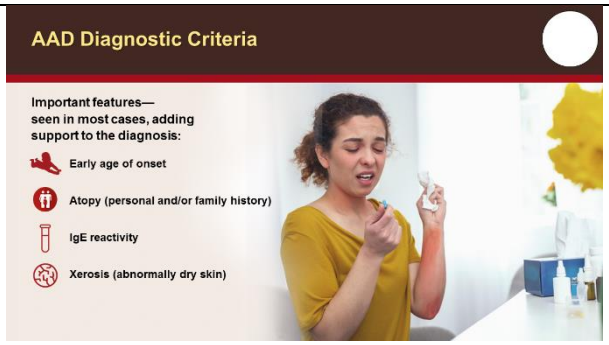
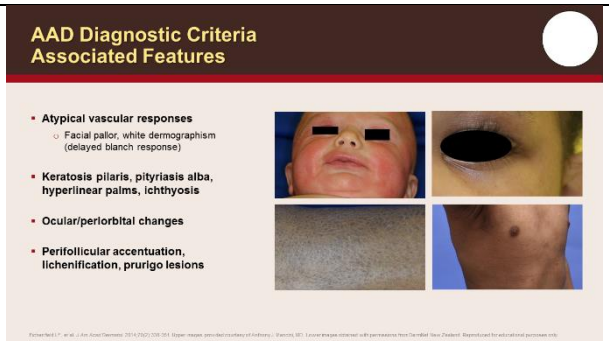
1		Hello and welcome to this module, Addressing the Global Burden of Atopic Dermatitis, Navigating Evolving Best Practices for Diagnosis and Treatment.
2		So I'm Tony Mancini. I'm a pediatric dermatologist in Chicago at Lurie Children's Hospital and Northwestern University Feinberg School of Medicine. And in this section, we're going to be discussing diagnosing and grading atopic dermatitis severity in pediatric and adult patients. We'll end the session with a few case vignettes with some questions so you can have some self-assessment.
3		So atopic dermatitis is a chronic pruritic inflammatory skin disease that occurs most often in the pediatric population, but clearly also occurs in adults. It's associated with an increased frequency of other atopic disorders: asthma in up to 25% of patients and allergic rhinitis up to about 40%. And it's really got a complex pathogenesis that has really been nicely unraveled over the last decade to decade-and-a-half, which involves genetic, immunologic, and environmental factors. And it's a combination of a dysfunctional epidermal permeability barrier in the skin and a dysregulated immune system and immune response in the

		deeper skin layers that really give rise to the clinical manifestations. As you all know, pruritus is the hallmark of atopic dermatitis. It's really responsible for a lot of the disease burden, both for patients but also for their families. And this itch, as we'll see is, is quite extreme and has impacts on other things like sleep, which really plays a large role in the quality-of-life impact. There's a variety of comorbidities in patients with atopic dermatitis. These include things like depression, anxiety, I mentioned sleep disturbance, and then, in the pediatric population, we also have to consider the increased prevalence of attention deficit disorder with hyperactivity.
4		So, if you look at the global prevalence, atopic dermatitis affects approximately 15% to 20% of children globally. As I mentioned, it tends to be a pediatric disease with 45% of patients experiencing the onset in the first 6 months of life, about 60% during the first year of life, and around 85% by 5 years of life. Now, while the majority of pediatric patients will go into a clinical remission, eventually, we do know that atopic dermatitis can persist in adolescents, young adults, and even older adults. And in some cases, they may arise for the first time in those populations. The prevalence overall of

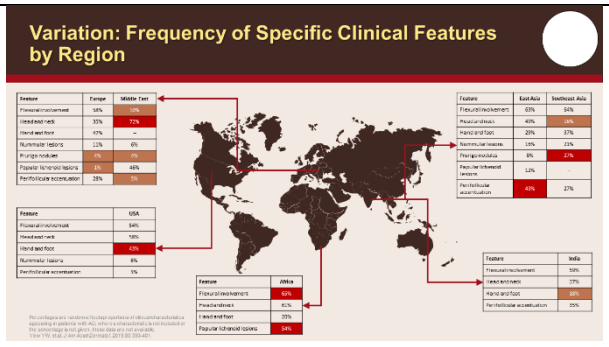
		atopic dermatitis in adults ranges between 1% to 10%; it really depends on the population that you're looking at. This number is believed to be around 7% in the United States, and 1 in 4 adults report that they had an adult-onset disease. You can see here in this graph that has color-coded the various prevalences according to this article back in 2018 around the world. You can see the United States with the prevalence around 10% to 15%, that's that light tan color, which is similar, also as you can see on the graph, in several parts of Europe, the far southern portion of Africa, and some areas of southeast Asia. If you look at the red, which is a very low prevalence of atopic dermatitis, that's especially prominent in Russia. And the predominantly high prevalence that you see in that, that darker brown color, over 20%, you see in a few select areas of South America, Africa, Europe, and the Middle East.
5		What about diagnostic criteria? Well, there's really a lack of universality in the various different published and validated diagnostic criteria. The most commonly used include the Hanifin-Rajka criteria, as you can see in the left-hand column here. This is the earliest form of atopic dermatitis criteria and they're still utilized in clinical trials. The American Academy of

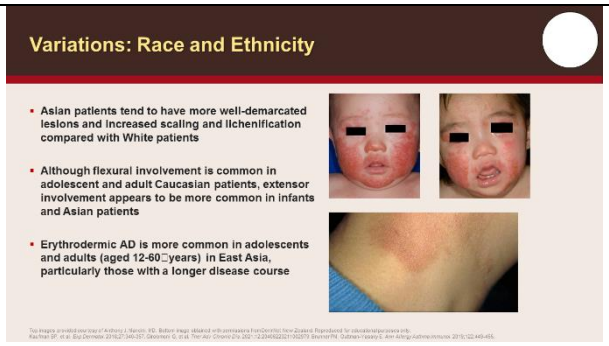
		Dermatology criteria published, I believe in 2014, is what's seen in the middle column and what we'll really focus on, because these are increasingly used to make the diagnosis, or at least for the sake of clinical trials. And then the United Kingdom Working Party has their own set of criteria which are listed in the far-right column. So, it's acknowledged that these criteria are not typically used in everyday practice, but they are utilized in the setting of clinical trials. And if you look at the middle column, the AAD criteria, so you see that there's central features, there's important features, and then there's associated features. And really to make the diagnosis, it's the essential features that are required, those important features lend diagnostic support, as do the associated features.
6		So essential features include itch; it's the *sine qua non* of atopic dermatitis. It's really required, and then eczema, which may be acute, subacute, or chronic forms. There's a typical morphology for the various presentations of eczema, and there are really age-specific patterns which we'll look at. There also has to be a history of a disease that is chronic or relapsing, which is really the nature, as we all know, of atopic dermatitis.

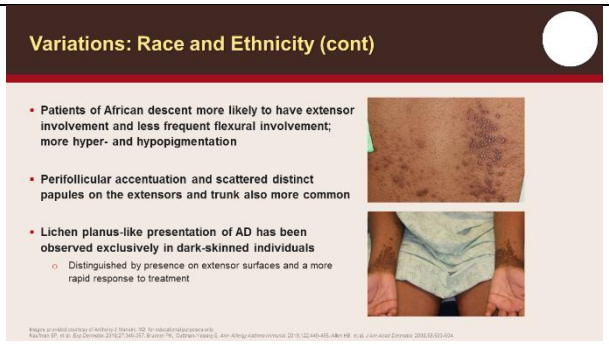
7		So, looking at eczema, what are the features you see clinically? This may include erythema, papules, excoriations from scratching, which you can see in the third photo over, and then lichenification, which is thickening of the skin that occurs from chronic trauma, chronic rubbing. So even if you have a family or a parent telling you that a child is not itchy or is not rubbing or scratching their skin, if you see plaques that are lichenified, you know that there is some form of external manipulation and repetitive rubbing or trauma that's causing that skin thickening.
8		What about the typical age-specific patterns? So, infants and younger children tend to have more extensor involvement, so that's the outer portions of the extremities, and facial involvement is quite common. As you get into toddlers and older kids and adults, then you get more of that antecubital and popliteal fossa involvement, as you see in the far-right photo at the bottom, which is what people think of when they think of atopic dermatitis. But in the infant population, you likely will not see that. It will be more extensor predominant. Adults tend to have more hand involvement, as you see in the middle photograph at the bottom, they tend to have more

		scalp involvement. And then the photo on the far left just shows typical infantile atopic dermatitis. You can see a lot of truncal involvement in this baby, and it's really highlighting the linear excoriations and the damage and the trauma that can be done to the skin from the marked itch. And that trauma further drives the epidermal barrier abnormalities, right, and just really drives this vicious cycle.
9		What about those important features? So, these are not required for the diagnosis, but they really add support to the diagnosis. So, an early age of onset, a history of atopy or other atopic disorders either in the patient or in the family. So, this includes things like allergic rhinoconjunctivitis, reactive airways disease, food allergy. IgE reactivity, which may be seasonal, related to allergens or related to food as allergens. And then xerosis, which is dry skin.
10		Looking at the associated features, so these are things that are common in these patients but are not required for diagnosis — facial pallor, especially common in infants and younger children — this is an atypical vascular response. If you look at the photograph in the upper left-hand corner, you see one of my patients with diffuse facial eczema. But

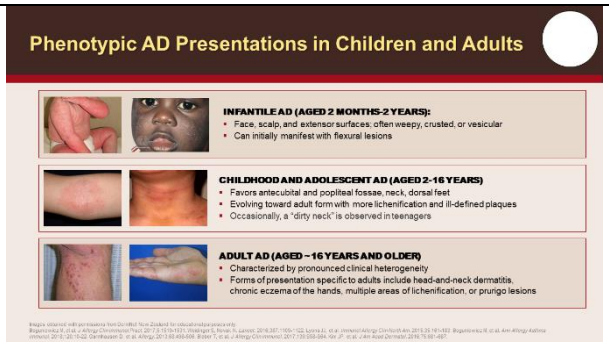
		what you notice is that there's this more of a pallor appearance and sparing of the mid-facial regions — the nose and the perioral areas — which is very common. That's been termed the headlight sign. It's really unclear why we see that kind of scarring. Pityriasis alba refers to the condition with hypopigmented macules and patches most predominantly on the face, which may be postinflammatory, but may also represent subclinical eczema. So, you don't really see the inflammation, but you get that temporary diminished pigmentation. Hyperlinearity of palms is really common in these patients, and then ichthyosis; this is the polygonal scaling or fish skin, if you will, which is really common in the form of ichthyosis vulgaris in patients with atopy. In the lower left-hand corner you see a beautiful example of that fish skin, that polygonal scaling. And ichthyosis vulgaris is really an important marker of atopic dermatitis and shares a pathologic feature, which we'll talk about as well. Ocular or periorbital changes are quite common. These may include, as you see in the picture in the upper right-hand corner of that hyperpigmentation, what's been called allergic shiners, but also, as you see a bit in this patient, those transverse pleats, those transverse creases below

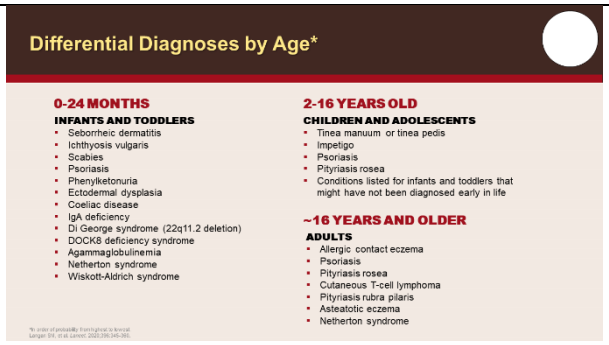
		the eye, which have been termed the Morgan–Dennie folds and a lot of this is made worse by the chronic eye rubbing and scratching that goes along with allergic conjunctivitis. Perifollicular accentuation is quite common, or follicular prominence, along with prurigo-like lesions, especially in our patients with skin of color. You see this more follicular or papular eczema appearance, as you see in the patient in the lower right-hand corner. And then we also will see things like lichenification, we talked about earlier, which is skin thickening from chronic trauma and prurigo lesions, which are focal areas of thickened skin and prurigo-like papules related to chronic scratching.
11		So here, we're looking at the variation in clinical features taken from a study published in 2019. You can see the world map here and just appreciate that there are variations based on geography. These aren't set in stone. These are nothing that are typically used for diagnostic confirmation, but they're just interesting. For instance, in the upper left-hand corner of that box, you can see that head and neck involvement, upwards of 72% of patients in the Middle East, but prurigo nodules and papular lesions are less common in Europe, for instance. In the lower left-hand box, you can see

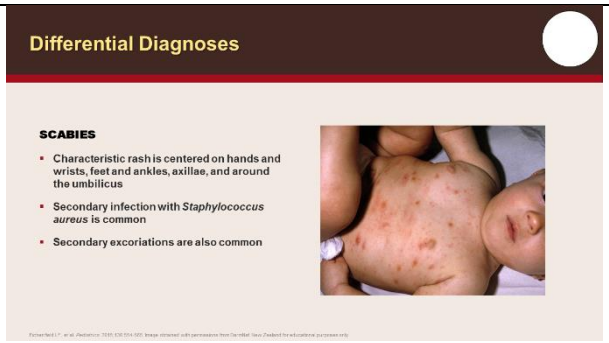
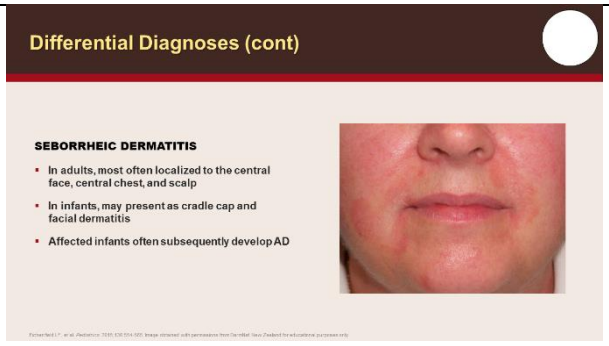
		hand-foot involvement in around 43% of patients in the United States. Circling down to the right, the Africa box at the bottom, flexural involvement around 65% of patients, papular lichenoid lesions around 54%. Now those lichenoid lesions are more typically seen in skin of color, so that would make sense geographically. The box in the upper right, you can see Eastern and Southeastern Asia: a high percentage of perifollicular accentuation in East Asia, prurigo nodules around a quarter of the patients in Southeast Asia. And then the box in the lower right looks at India: flexural involvement around 60%, hand and foot involvement in around 1 out of 5. So again, just interesting to see the geographic variations in the disease.
12		It's known that Asian patients tend to have more well-demarcated lesions, more scaling, and lichenification compared to White patients, for instance. The patients in the upper two panels are two of my Asian infants, with more moderate-to-severe atopic dermatitis. And what you can really appreciate is the sharp demarcation and these plaques on the face. And again, although both of them have a little bit of nose involvement, you can see mostly sparing in that mid-facial region, again that headlight sign. And although flexural involvement is

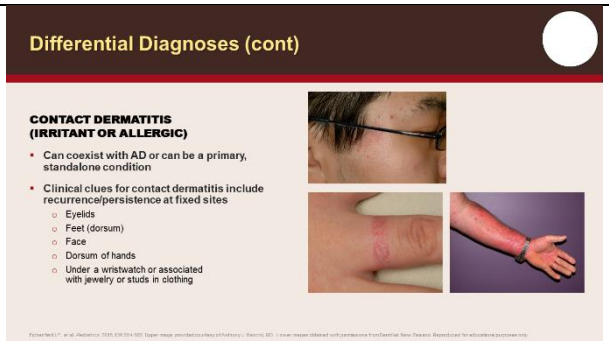
		common in both adolescent and adult Caucasian patients, it seems that a more extensor predominance is seen in a majority of Asian patients. Erythrodermic atopic dermatitis — diffuse involvement of erythema — is more common in adolescent and adults in East Asia, and especially those that have had a more chronic disease course. And the photograph at the bottom really just shows lichenification, sharp demarcation, but this plaque that you know, has been rubbed fairly chronically to develop that type of lichenification.
13		Now patients with African descent are more likely to have extensor involvement, and less frequently flexural involvement. And this population has much more prominence of pigmentary changes, both hypo- and especially hyperpigmentation. Perifollicular accentuation, or what we call follicular or papular eczema, much more common in skin of color, and the photograph in the upper right panel really shows that papular follicular prominence. You even see that the background skin seems to have follicular prominence. It looks like goosebumps, but they don't go away. This is much more common in skin of color. And then there's a lichen planus-like presentation, which is more violaceous to

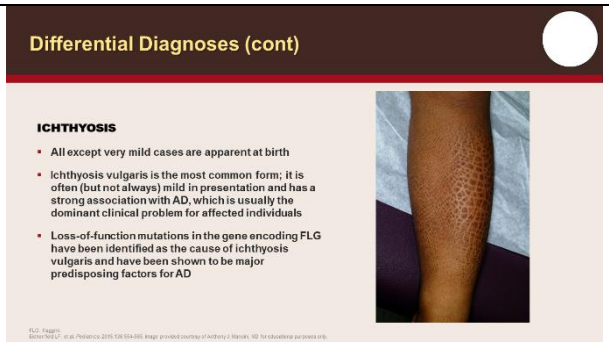
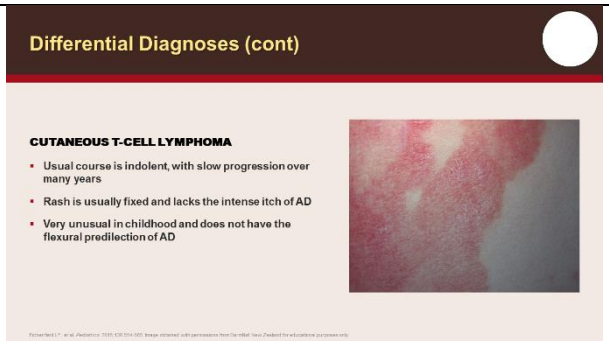
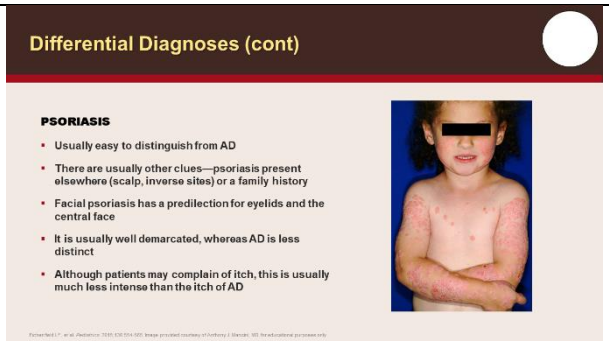
		brown. You may see more of these polygonal flat-topped plaques, and really it's observed exclusively in patients with skin of color, primarily Black patients. And although it's most commonly seen on extensor surfaces, my patient in the lower panel here, this photograph is showing you volar forearm involvement with a very lichen-like appearance.
14		Remember that erythema in darker skin tones may be more difficult to appreciate. Look at the photograph on the far right. This is a Black patient of mine with atopic dermatitis, but you really have more of a difficult time appreciating the erythema. This is important because a lot of the scoring systems rely on erythema as one component, so you may be underestimating that component if you don't look very carefully. The patient on the left, you can really see the erythema, this is a patient of skin of color again, and here this really highlights lichenification with excoriations, erosions, and crusting. That's staphylococcal superinfection until proven otherwise.

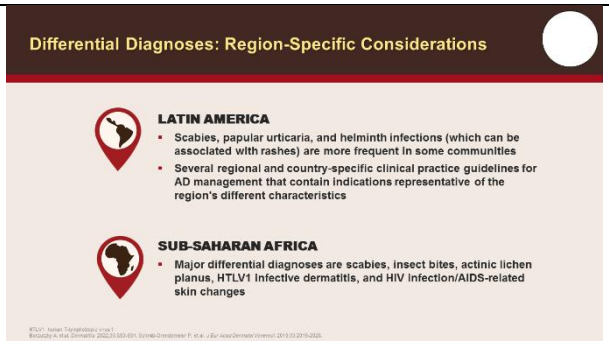
15		So, phenotypic presentations in children and adults, just to recap, infantile atopic dermatitis, most commonly extensor surfaces, the face, you may see scalp involvement, it may look more weepy, more exudative, crusted, even sometimes vesicular. Now remember, though, that infants occasionally will present with flexural involvement. So, toddlers, older children, adolescents, now you get more into the antecubital and popliteal regions, you can see here on the left photograph an example of antecubital involvement, and more neck involvement, as you can see here on the far-right photo. You may also see more involvement of dorsal feet. This really evolves more towards an adult form of atopic dermatitis. And as kids get better at scratching and rubbing, you're going to see more lichenification; that goes hand in hand. Sometimes you'll see a dirty neck presentation in teens, which may represent severe xerosis. It might just be retention hyperkeratosis from not scrubbing those regions during bathing. It might even be ichthyosis vulgaris, or other forms of ichthyosis. And then adult disease. You can see more of the hand involvement, as you see in the lower right-hand photograph. Again, more lichenification, the patient on the lower left-hand photograph has

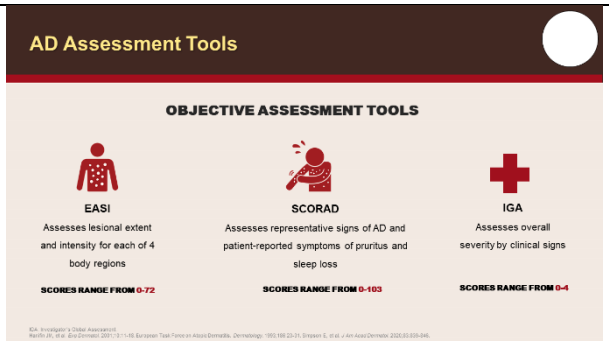
		crusting again, suggestive of secondary superinfection.
16		Although atopic dermatitis is a fairly straightforward diagnosis, there is a differential diagnosis which is shown on this screen. On the left-hand column, we're seeing infants and toddlers, so things like seborrheic dermatitis, which may be in the differential or may coexist along with atopic dermatitis. We talked about ichthyosis vulgaris, sometimes scabies — especially the more Norwegian or crusted form — can mimic atopic dermatitis. Psoriasis sometimes can be difficult to distinguish, although there are a few distinguishing features in the infant populations, such as involvement of the diaper region, which you should not see with atopic dermatitis, involvement of the umbilical region. There's nutritional disorders on this list; you see some ectodermal dysplasia, you see some nutritional deficiencies. These are all going to be far, far, far less common, but need to be included in the differential, especially in patients who have more severe disease that is resistant to treatment. On the right-hand side, in the upper portion we see children and adolescents, so tinea may be in the differential, impetigo sometimes, again psoriasis, or other papulosquamous disorders

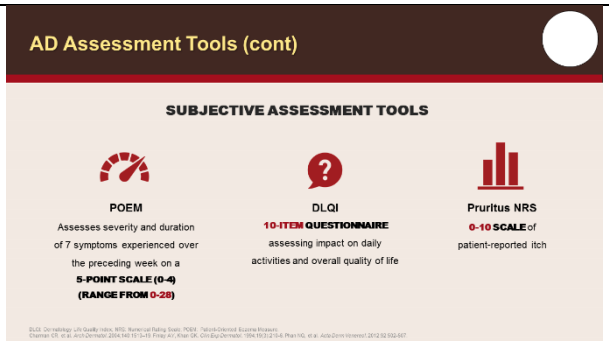
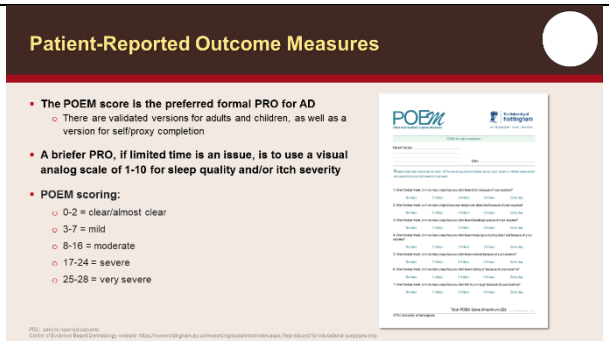
		like pityriasis. And the lower right-hand area lists the differential in adult patients. So, allergic contact dermatitis becomes more common, commonly a differential. Here again you see papulosquamous disorders and then you see here cutaneous T-cell lymphoma, so mycosis fungoides, which should be in the differential of older patients that have dermatitis that's not improving with the expected therapy.
17		So, let's look at just a few of these: Scabies, I think most know how to recognize scabies, papules, especially in flexural regions, armpits, palms, and soles, the groin, the genitalia, and the web spaces. But sometimes it can be quite crusty or more diffuse, a form called Norwegian scabies that can look very dermatitic. Have a high suspicion, especially in patients that have immunodeficiency or have immunologic impairment and present with resistant dermatitis. You may see secondary infection with Staph in this setting as well.
18		Seborrheic dermatitis: Here's classic seb-derm with nasolabial fold involvement in an older patient. But remember, in infants you might see cradle cap presentation, you might see involvement of the face and the hair-bearing regions, and, like psoriasis, you may see involvement of the diaper area and the

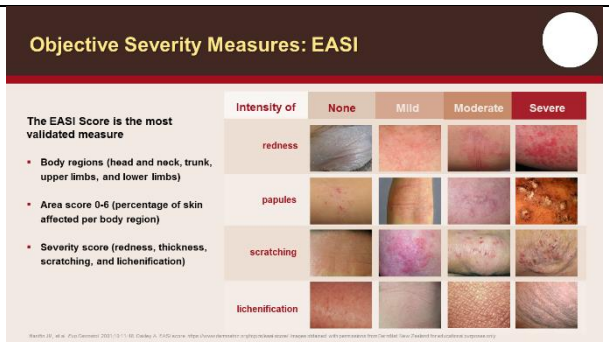
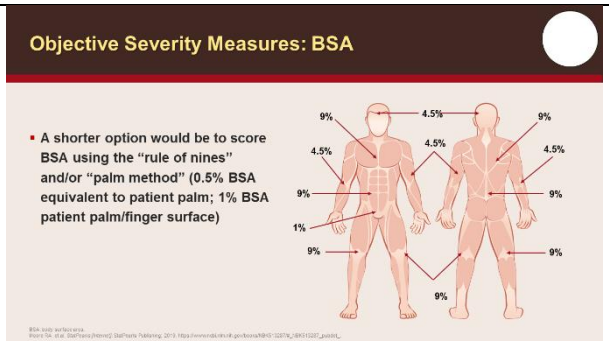
		umbilicus, which really helps you distinguish it from atopic dermatitis.
19		Contact dermatitis: This can coexist with atopic dermatitis, or it might exist on its own as a standalone condition. Think about it if there are recognizable patterns or distribution in areas of known exposures, as you see in these photographs. The upper photograph of a boy reacting to nickel in the metal of the arm of his glasses, you can see that temple dermatitis. The lower left-hand corner, obviously related to metal in the ring. You can see the sharp demarcation, which corresponds to the exposure to the metal. And on the far-right lower corner, a patient with a more diffuse forearm dermatitis that really was all triggered by allergic contact to nickel, again, in the watch band. So clinical clues for contact dermatitis might include resistance to treatment or recognizable locations or patterns. Think about eyelids, dorsal feet, facial involvement, especially with more resistant dermatitis, dorsal hands, or under jewelry, like I'm showing you here. I'm not showing you earrings, but that's another obvious potential site of ACD to nickel.

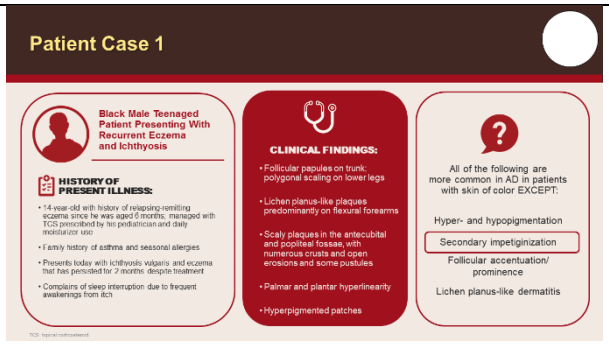
20		Ichthyosis we talked about. Here's one of my younger patients with a beautiful example of ichthyosis vulgaris on the lower legs. Remember, this is that classic polygonal scaling. It looks like a mud pond that is drying and starting to crack, right? And this is a marker for atopy. Often goes along with atopic dermatitis and also a marker for a filaggrin mutation, which is a key protein in our upper epidermis. And filaggrin mutations can give rise to ichthyosis vulgaris and more severe atopic dermatitis — these are loss-of-function mutations.
21		Here's an older patient with cutaneous T-cell lymphoma. So I would have expected to hear that this patient was resistant to therapy. Subsequently, a skin biopsy was performed, which, combining the histology and the immunophenotyping, was consistent with CTCL. Less common in pediatric patients, and when we do see it, it's more often in patients with skin of color and presents in a hypopigmented presentation.
22		And here's one of my young patients with psoriasis. You can really appreciate the sharp demarcation of these lesions, that silvery white micaceous scale which we talk about with psoriasis. Facial involvement is not unusual, especially the eyelids, and often the

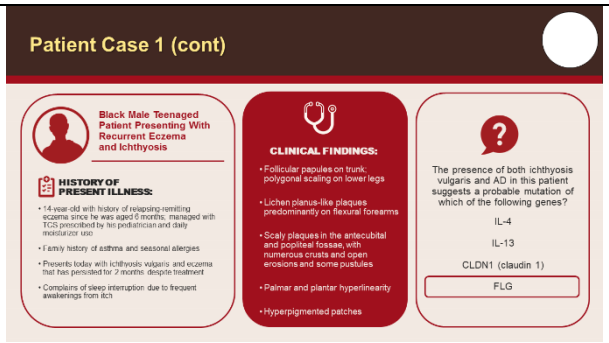
		central face, although here you see more of a peripheral presentation, like atopic dermatitis. You can really appreciate the involvement at the hairline with these really micaceous, scaly erythematous plaques. And psoriasis often has a predilection for extensor surfaces and especially areas over sites of trauma, so folds over joints like the elbow regions, the hips, the knees, all common locations for psoriasis. Itch is expected to be far less common in psoriasis, although it is present, but typically not as severe as in atopic dermatitis.
23		Is there a difference in the differential based regionally or geographically? Well in Latin America you might think about other diagnoses being more common like scabies, papular, urticaria, helminthic infections, which can be associated with a variety of rashes. And there are several regional-specific clinical practice guidelines that might include consideration for diseases that are more common in that geographical location. In sub-Saharan Africa, the differential again includes scabies, insect bite reactions, actinic lichen planus, a form of lichen planus that's triggered by sunlight or human T-cell lymphotropic virus type 1 infective dermatitis or another HTLV, HTLV-3 or HIV infection, and age-related skin changes. So

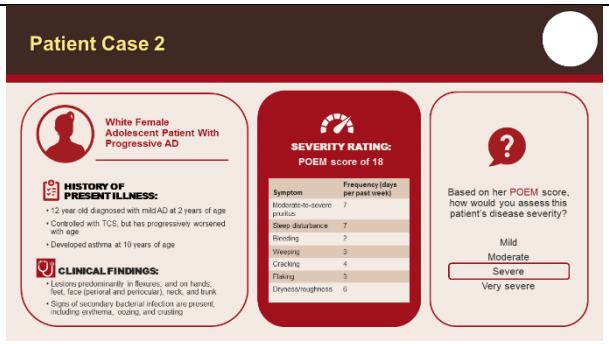
		geographically, there might be some changes based on the diseases that are more inherent to that population.
24		What about assessment tools for severity? There's a variety of these. So the EASI score — that's the Eczema Area and Severity Index — is utilized a lot in clinical trials. It assesses lesional extent and intensity for each of four body regions, and the scores here range between 0 and 72. The SCORAD in the middle — that's the Scoring Atopic Dermatitis measure — this assesses representative signs of atopic dermatitis and patient-reported outcomes or symptoms, including itch and sleep loss. And the range of the scores here is 0 to 103. The Investigator Global Assessment — the IGA score — another commonly used measure in clinical trials. This assesses the overall severity by clinical signs, with scores from 0 to 4. So 0 is clear, 1 is almost clear, and then 2 thru 4 are mild, moderate, and severe. This is a very important measure because it's often utilized in clinical trials and by the FDA to identify a primary endpoint of a treatment on a disease, where typically patients have to have a score of 0 or 1, clear or almost clear, and often in clinical trials have to also have a 2-grade improvement in that score. So that would be from a 4 to a 2 or better or from a 3 to a

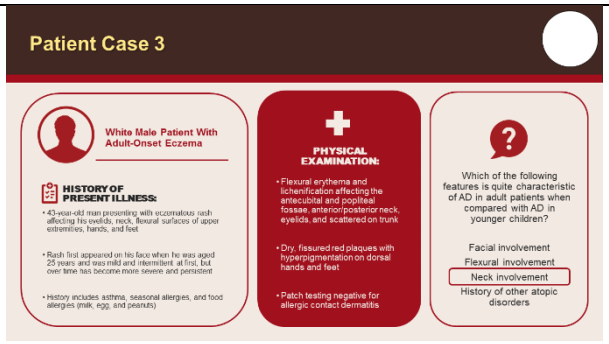
		1 or better, in order to meet an endpoint.
25		The POEM score — that's the Patient-Oriented Eczema Measure. Now this is the one we use most commonly in the clinical setting. We keep these in our clinic. We utilize them in nearly all patients, and it really helps us justify the need for treatment to insurers when we're trying to get newer therapies. This assesses severity and duration of seven different symptoms experienced over the preceding week, and it's a 5-point scale where they get a ranking of 0 to 4. So, the scores will range from 0 to 28, and we'll show you that range in a minute. The Dermatology Life Quality Index — or DLQI — this is a 10-item questionnaire that assesses impact on daily activities and overall quality of life. And the Pruritus NRS, the numerical rating scale, also utilized a lot in clinical trials, it's a 0-to-10 scale of patient-reported itch.
26		So, here's the POEM score. This you can easily print off of the internet. You can see it on the far right. It's the preferred formal patient-related outcomes for atopic dermatitis. I'm sorry, patient-reported outcomes. And there are validated versions of the POEM score, both for adults and children. There's a briefer patient-reported outcome, like using just a visual analog scale from 1 to 10 for sleep

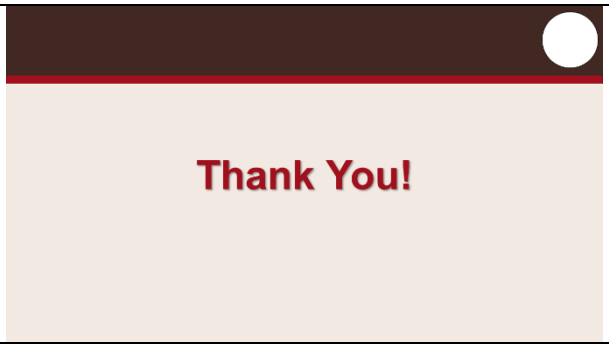
		quality and itch severity, but I find the POEM score very easy to do. It takes us no longer than about 1 to 2 minutes. So, when you look at POEM scoring, you can see it here listed on the bottom on the left-hand side. And I will highlight that 8 to 16 is moderate, 17 to 24 severe, and 25 to 28 very severe, and this really helps you justify disease severity for authorization of newer treatment options.
27		The EASI score we talked about, so it's the most validated measure. It breaks it down by body region. Then there's an area score for each of those regions. Looking at the percentage of involvement of that region and the severity score is based on redness, papules, scratching, and lichenification. And as you can see in this chart, they're ranked from none to severe.
28		A shorter option is just to look at body surface area of involvement. We all remember the rule of nines from our medical training or the palm method, where the palm itself represents 0.5% body surface area. The entire hand, if you include the fingers, would be 1% body surface area, and you can see the rule of nines here. Here's the pictorial, the trunk being 9%. Both front and back, the extremity is the upper 4.5%, both for front and back. The lower extremities 9% front, 9% back, the head 4.5%. So,

		you add these all up, it does come to 100%. That would be a quick approach, but I really prefer doing the POEM score.
29		All right, let's end with some cases. So, I'm going to read the case and then we're going to read the potential answer choices, and then you're going to go ahead and select your choice before I reveal the correct response. So, Case 1. This is a 14-year-old Black male, a teenager who has a history of relapsing and remitting next month since he was 6 months of age. He's been managed with topical corticosteroids prescribed by his pediatrician and daily use of moisturizers. There's a family history of asthma and seasonal allergies, and he presents today with classic eczematous skin lesions and ichthyosis vulgaris. And he states these have been really persistent for the last couple of months despite compliance with therapy. He complains about sleep interruption and frequent awakenings because of his marked itch. On examination, you notice follicular papules on his trunk, polygonal scaling on his lower legs, he has lichen planus-like plaques on the flexural forearms predominantly, scaly plaques, and his antecubital and popliteal regions, lots of crusting, open erosions, and some pustules. He has hyperlinearity of his palms

		and soles, and he has a variety of hyperpigmented patches, postinflammatory changes from prior involvement. All right, the question for this patient on the lower right. All of the following are more common in atopic dermatitis patients with skin of color except for hyper- and hypopigmentation, secondary impetiginization, follicular accentuation or prominence, lichen planus-like dermatitis. So go ahead and take a few seconds here to consider an answer. All right. And the correct response here is secondary impetiginization; clearly pigmentary alteration, the follicular prominence, follicular eczema, follicular accentuation, and that lichen planus-like dermatitis are all more common in patients with skin of color.
30		All right. So, the presence of both ichthyosis vulgaris and atopic dermatitis in this patient suggests a probable mutation in which of the following genes: Interleukin 4? Interleukin 13? CLDN1 which encodes claudin 1, or FLG, which encodes filaggrin. Go ahead and make your choice. And the correct response here is filaggrin. Remember we talked about filaggrin mutations being more common in the setting of ichthyosis vulgaris and more severe atopic dermatitis. Filaggrin encodes a very important protein in the upper epidermis and its

		breakdown products actually help retain moisture in our epidermal barrier. Those have been called natural moisturizing factors.
31		All right, Case 2. It's a 12-year-old White female diagnosed with mild atopic dermatitis at 2 years of age. She's been fairly well controlled with corticosteroids in the past, but it's progressively worsened as she's gotten older. She developed asthma at 10 years of age. Clinical findings include lesions predominantly in the flexures on her hands, feet, and face, including perioral and periorbital locations, her neck, and her trunk. And she has a lot of signs of secondary superinfection — she has crusting, erythema, and oozing. Her POEM score is 18 and you can see it broken down here, the responses that were given. So based on her POEM score, how would you assess her disease severity? Her overall score is 18. Is she mild, moderate, severe, or very severe? And by the way, those numbers in that middle table you don't add those up to get the score. We're just telling you the frequency of days. Remember the score is from 0 to 4 based on your response. All right. So, a POEM score of 18. Hopefully you remember that that puts her into the severe category. OK. So, between 18 and 24 is severe and 25 to 28 would be considered

		very severe, 8 to 16 moderate. And then below that would be mild.
32		All right, Case 3. A 43-year-old man presents with an eczematous rash affecting his eyelids, neck, flexural surfaces of his upper extremities, his hands, and his feet. The rash first appeared on his face when he was around 25 years of age and it was mild and intermittent at first, but it has become more severe and more persistent. His history includes asthma and seasonal allergies and food allergy, including milk, eggs, and peanuts, which he does avoid. Physical exam reveals flexural erythema lichenification involving the antecubital and popliteal regions, anterior/posterior neck, eyelids, and scattered on his trunk. He has dry fissure, red plaques with hyperpigmentation on his dorsal hands and feet, and he has had patch testing, which was negative for allergens causing allergic contact dermatitis. So, the question. Which of the following features is quite characteristic of atopic dermatitis in adult patients when compared to a topic dermatitis in younger children? Is it facial involvement? Flexural involvement? Neck involvement? Or a history of other atopic disorders? Go ahead and consider the options and make your choice. All right, the answer here would be neck

		involvement. And really it distinguishes older children, adolescents, I should say, and adults from younger children, although anybody can get any of these locations, obviously.
33		Well, thank you very much for your attention. I hope you enjoyed this module.