2024 Eastern Allergy Conference

Patch Testing is Underutilized in Atopic Dermatitis

CON

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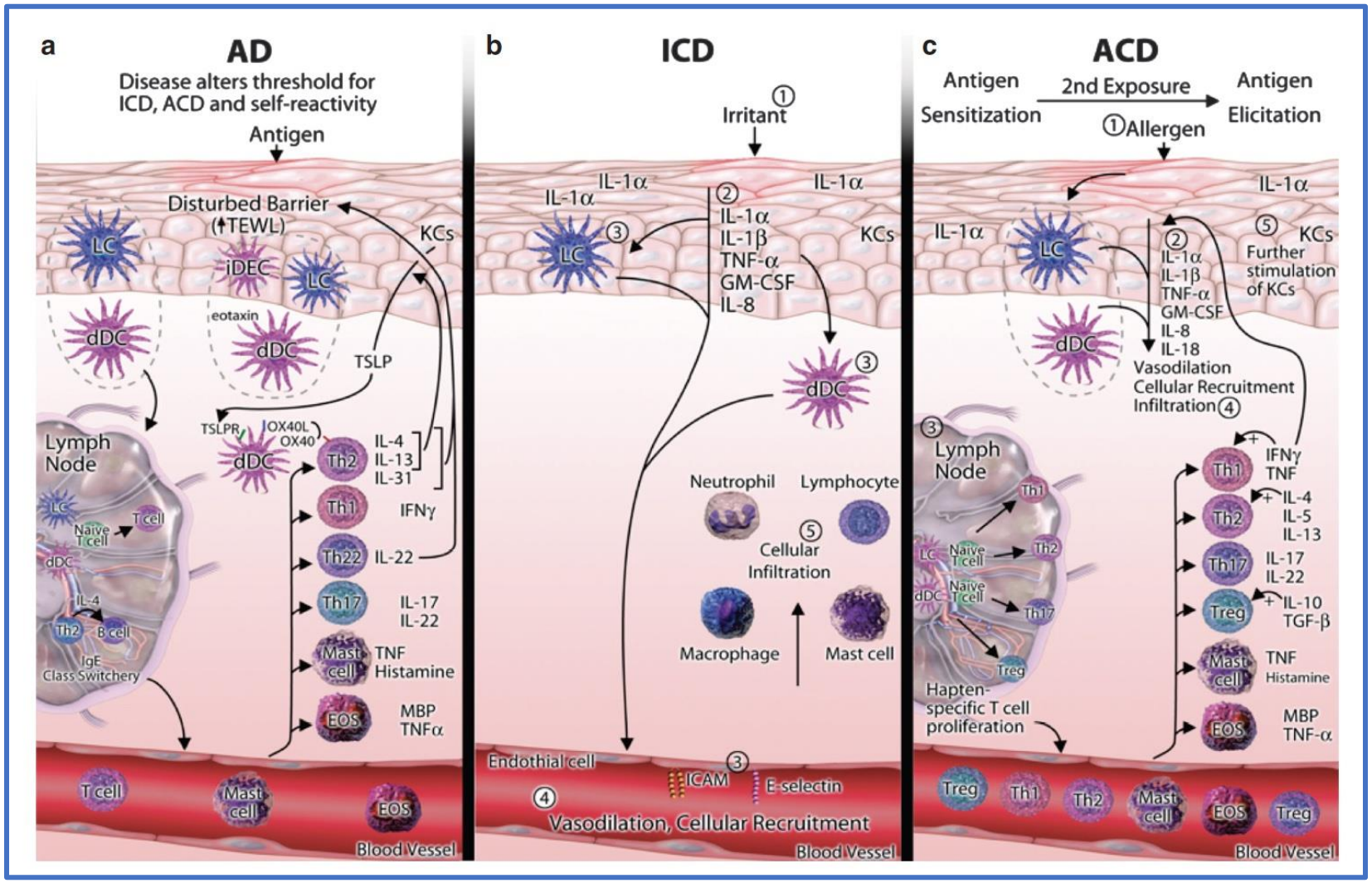
Learning Objectives

Upon completion of this learning activity, participants should be able to:

1. Correctly diagnose atopic dermatitis and recognize the differential diagnosis of eczematous rashes

2. Manage patients with chronic eczematous rash with appropriate testing if needed

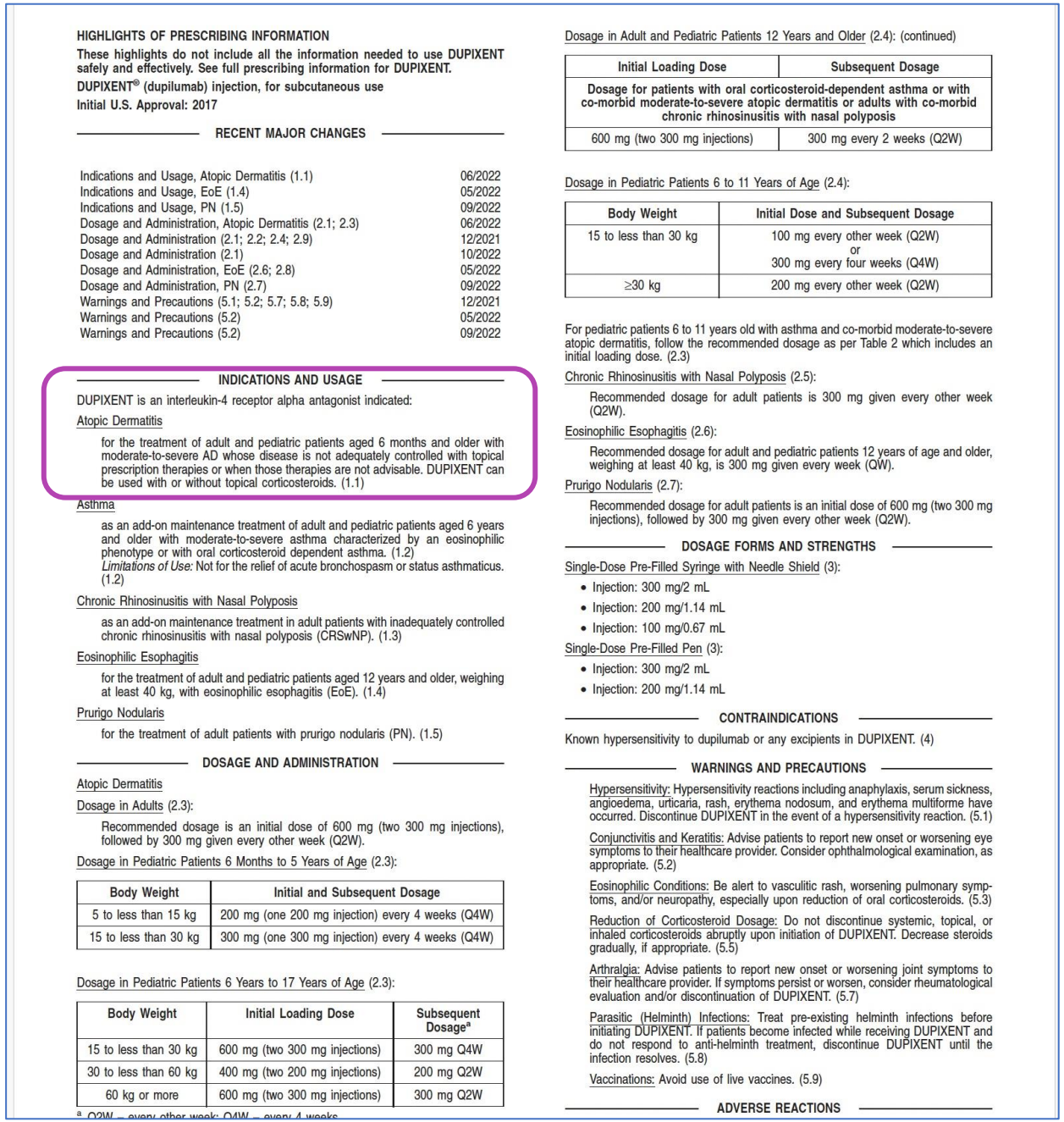
Immunology of AD vs ACD



Gittler JK, et al. J Allergy Clin Immunol 2013;131:300

Dupilumab PI

pgs 1-20: 0 “patch testing”



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DUPIXENT safely and effectively. See full prescribing information for DUPIXENT.

DUPIXENT® (dupilumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

RECENT MAJOR CHANGES

Indications and Usage, Atopic Dermatitis (1.1)	06/2022
Indications and Usage, EoE (1.4)	05/2022
Indications and Usage, PN (1.5)	09/2022
Dosage and Administration, Atopic Dermatitis (2.1; 2.3)	06/2022
Dosage and Administration (2.1; 2.2; 2.4; 2.9)	12/2021
Dosage and Administration (2.1)	10/2022
Dosage and Administration, EoE (2.6; 2.8)	05/2022
Dosage and Administration, PN (2.7)	09/2022
Warnings and Precautions (5.1; 5.2; 5.7; 5.8; 5.9)	12/2021
Warnings and Precautions (5.2)	05/2022
Warnings and Precautions (5.2)	09/2022

INDICATIONS AND USAGE

DUPIXENT is an interleukin-4 receptor alpha antagonist indicated:

Atopic Dermatitis

for the treatment of adult and pediatric patients aged 6 months and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids. (1.1)

Asthma

as an add-on maintenance treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma. (1.2)
Limitations of Use: Not for the relief of acute bronchospasm or status asthmaticus. (1.2)

Chronic Rhinosinusitis with Nasal Polyposis

as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP). (1.3)

Eosinophilic Esophagitis

for the treatment of adult and pediatric patients aged 12 years and older, weighing at least 40 kg, with eosinophilic esophagitis (EoE). (1.4)

Prurigo Nodularis

for the treatment of adult patients with prurigo nodularis (PN). (1.5)

DOSAGE AND ADMINISTRATION

Atopic Dermatitis

Dosage in Adults (2.3):

Recommended dosage is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week (Q2W).

Dosage in Pediatric Patients 6 Months to 5 Years of Age (2.3):

Body Weight	Initial and Subsequent Dosage
5 to less than 15 kg	200 mg (one 200 mg injection) every 4 weeks (Q4W)
15 to less than 30 kg	300 mg (one 300 mg injection) every 4 weeks (Q4W)

Dosage in Pediatric Patients 6 Years to 17 Years of Age (2.3):

Body Weight	Initial Loading Dose	Subsequent Dosage[a]
15 to less than 30 kg	600 mg (two 300 mg injections)	300 mg Q4W
30 to less than 60 kg	400 mg (two 200 mg injections)	200 mg Q2W
60 kg or more	600 mg (two 300 mg injections)	300 mg Q2W

[a] Q2W = every other week; Q4W = every 4 weeks

Dosage in Adult and Pediatric Patients 12 Years and Older (2.4): (continued)

Initial Loading Dose	Subsequent Dosage
Dosage for patients with oral corticosteroid-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis or adults with co-morbid chronic rhinosinusitis with nasal polyposis	
600 mg (two 300 mg injections)	300 mg every 2 weeks (Q2W)

Dosage in Pediatric Patients 6 to 11 Years of Age (2.4):

Body Weight	Initial Dose and Subsequent Dosage
15 to less than 30 kg	100 mg every other week (Q2W) or 300 mg every four weeks (Q4W)
≥30 kg	200 mg every other week (Q2W)

For pediatric patients 6 to 11 years old with asthma and co-morbid moderate-to-severe atopic dermatitis, follow the recommended dosage as per Table 2 which includes an initial loading dose. (2.3)

Chronic Rhinosinusitis with Nasal Polyposis (2.5):

Recommended dosage for adult patients is 300 mg given every other week (Q2W).

Eosinophilic Esophagitis (2.6):

Recommended dosage for adult and pediatric patients 12 years of age and older, weighing at least 40 kg, is 300 mg given every week (QW).

Prurigo Nodularis (2.7):

Recommended dosage for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week (Q2W).

DOSAGE FORMS AND STRENGTHS

Single-Dose Pre-Filled Syringe with Needle Shield (3):

- Injection: 300 mg/2 mL
- Injection: 200 mg/1.14 mL
- Injection: 100 mg/0.67 mL

Single-Dose Pre-Filled Pen (3):

- Injection: 300 mg/2 mL
- Injection: 200 mg/1.14 mL

CONTRAINDICATIONS

Known hypersensitivity to dupilumab or any excipients in DUPIXENT. (4)

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions including anaphylaxis, serum sickness, angioedema, urticaria, rash, erythema nodosum, and erythema multiforme have occurred. Discontinue DUPIXENT in the event of a hypersensitivity reaction. (5.1)

Conjunctivitis and Keratitis: Advise patients to report new onset or worsening eye symptoms to their healthcare provider. Consider ophthalmological examination, as appropriate. (5.2)

Eosinophilic Conditions: Be alert to vasculitic rash, worsening pulmonary symptoms, and/or neuropathy, especially upon reduction of oral corticosteroids. (5.3)

Reduction of Corticosteroid Dosage: Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of DUPIXENT. Decrease steroids gradually, if appropriate. (5.5)

Arthralgia: Advise patients to report new onset or worsening joint symptoms to their healthcare provider. If symptoms persist or worsen, consider rheumatological evaluation and/or discontinuation of DUPIXENT. (5.7)

Parasitic (Helminth) Infections: Treat pre-existing helminth infections before initiating DUPIXENT. If patients become infected while receiving DUPIXENT and do not respond to anti-helminth treatment, discontinue DUPIXENT until the infection resolves. (5.8)

Vaccinations: Avoid use of live vaccines. (5.9)

ADVERSE REACTIONS

Differential diagnosis of AD

Congenital disorders
- Netherton's syndrome

Chronic dermatoses
- Seborrheic dermatitis
- Contact dermatitis (allergic or irritant)
- Nummular eczema
- Lichen simplex chronicus

Infections and infestations
- Scabies
- HIV-associated dermatitis

Malignancy
- Cutaneous T cell lymphoma (mycosis fungoides/Sézary syndrome)

Immunodeficiencies
- Wiskott-Aldrich syndrome
- SCID
- Hyper-IgE syndrome
- *DOCK8* mutations
- IPEX

Metabolic disorders
- Zinc deficiency
- Pyridoxine (vitamin B_6) and niacin deficiency
- Multiple carboxylase deficiency
- Phenylketonuria

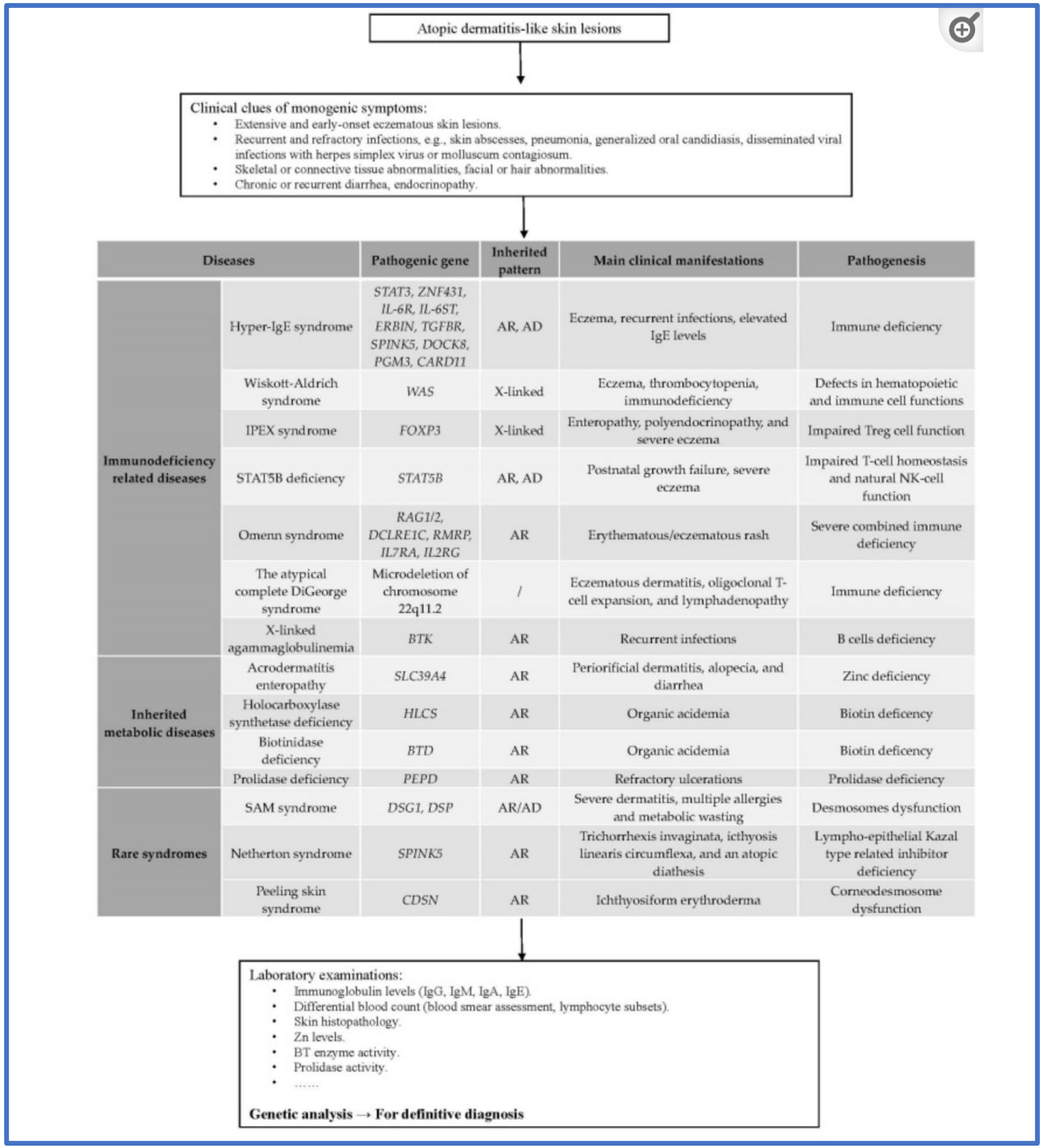
Proliferative disorder
- Letterer-Siwe disease

Boguniewicz M, et al. Middleton's Allergy

Thorough work up for every recalcitrant AD patient?

- Eval of hair for trichorrhexis invaginate & genetic testing for *SPINK5* mutations
- Patch testing
- Microscopic eval of skin scrapings
- Antigen/antibody test HIV
- Multiple biopsies to r/o CTCL
- Genetic testing for WAS, SCID, HIE, DOCK8, IPEX
- Zinc levels
- Testing of skin cells to determine pyruvate carboxylase enzyme activity
- Skin biopsy & skeletal survey

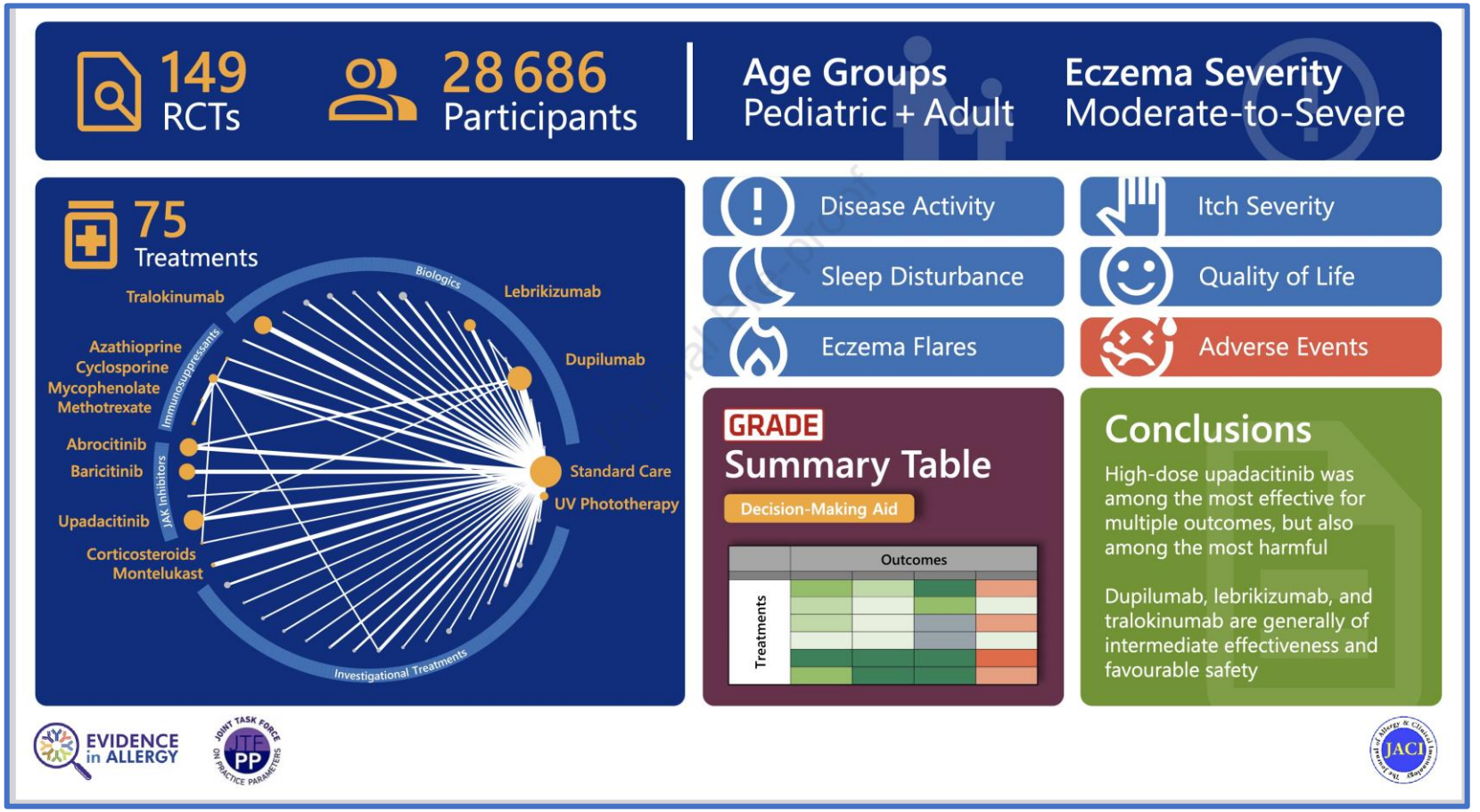
Atopic Dermatitis-like Genodermatosis: Disease Diagnosis and Management



Diseases		Pathogenic gene	Inherited pattern	Main clinical manifestations	Pathogenesis
Immunodeficiency related diseases	Hyper-IgE syndrome	*STAT3, ZNF431, IL-6R, IL-6ST, ERBIN, TGFBR, SPINK5, DOCK8, PGM3, CARD11*	AR, AD	Eczema, recurrent infections, elevated IgE levels	Immune deficiency
	Wiskott-Aldrich syndrome	*WAS*	X-linked	Eczema, thrombocytopenia, immunodeficiency	Defects in hematopoietic and immune cell functions
	IPEX syndrome	*FOXP3*	X-linked	Enteropathy, polyendocrinopathy, and severe eczema	Impaired Treg cell function
	STAT5B deficiency	*STAT5B*	AR, AD	Postnatal growth failure, severe eczema	Impaired T-cell homeostasis and natural NK-cell function
	Omenn syndrome	*RAG1/2, DCLRE1C, RMRP, IL7RA, IL2RG*	AR	Erythematous/eczematous rash	Severe combined immune deficiency
	The atypical complete DiGeorge syndrome	Microdeletion of chromosome 22q11.2	/	Eczematous dermatitis, oligoclonal T-cell expansion, and lymphadenopathy	Immune deficiency
	X-linked agammaglobulinemia	*BTK*	AR	Recurrent infections	B cells deficiency
Inherited metabolic diseases	Acrodermatitis enteropathy	*SLC39A4*	AR	Periorificial dermatitis, alopecia, and diarrhea	Zinc deficiency
	Holocarboxylase synthetase deficiency	*HLCS*	AR	Organic acidemia	Biotin deficency
	Biotinidase deficiency	*BTD*	AR	Organic acidemia	Biotin deficency
	Prolidase deficiency	*PEPD*	AR	Refractory ulcerations	Prolidase deficiency
Rare syndromes	SAM syndrome	*DSG1, DSP*	AR/AD	Severe dermatitis, multiple allergies and metabolic wasting	Desmosomes dysfunction
	Netherton syndrome	*SPINK5*	AR	Trichorrhexis invaginata, icthyosis linearis circumflexa, and an atopic diathesis	Lympho-epithelial Kazal type related inhibitor deficiency
	Peeling skin syndrome	*CDSN*	AR	Ichthyosiform erythroderma	Corneodesmosome dysfunction

Pan C, et al. Diagnostics 2022:12:2177

Systemic treatments for atopic dermatitis (eczema): systematic review and network meta-analysis of randomized trials



J Allergy Clin Immunol 2023; 152:1470

Linked systematic review and network meta-analysis showed that...

- ... compared to continued standard topical treatment alone, adding dupilumab or tralokinumab led to improvements in multiple patient-important outcomes including AD severity, judged either by patients or clinicians, itch, sleep disturbance, without an increase in serious AE or AE leading to discontinuation
- ... patients with AD value stepping-up therapy based on severity, safe medications, relief and normalization of daily activities, and a strong patient-provider relationship, despite the need for injections and potential fear of needles

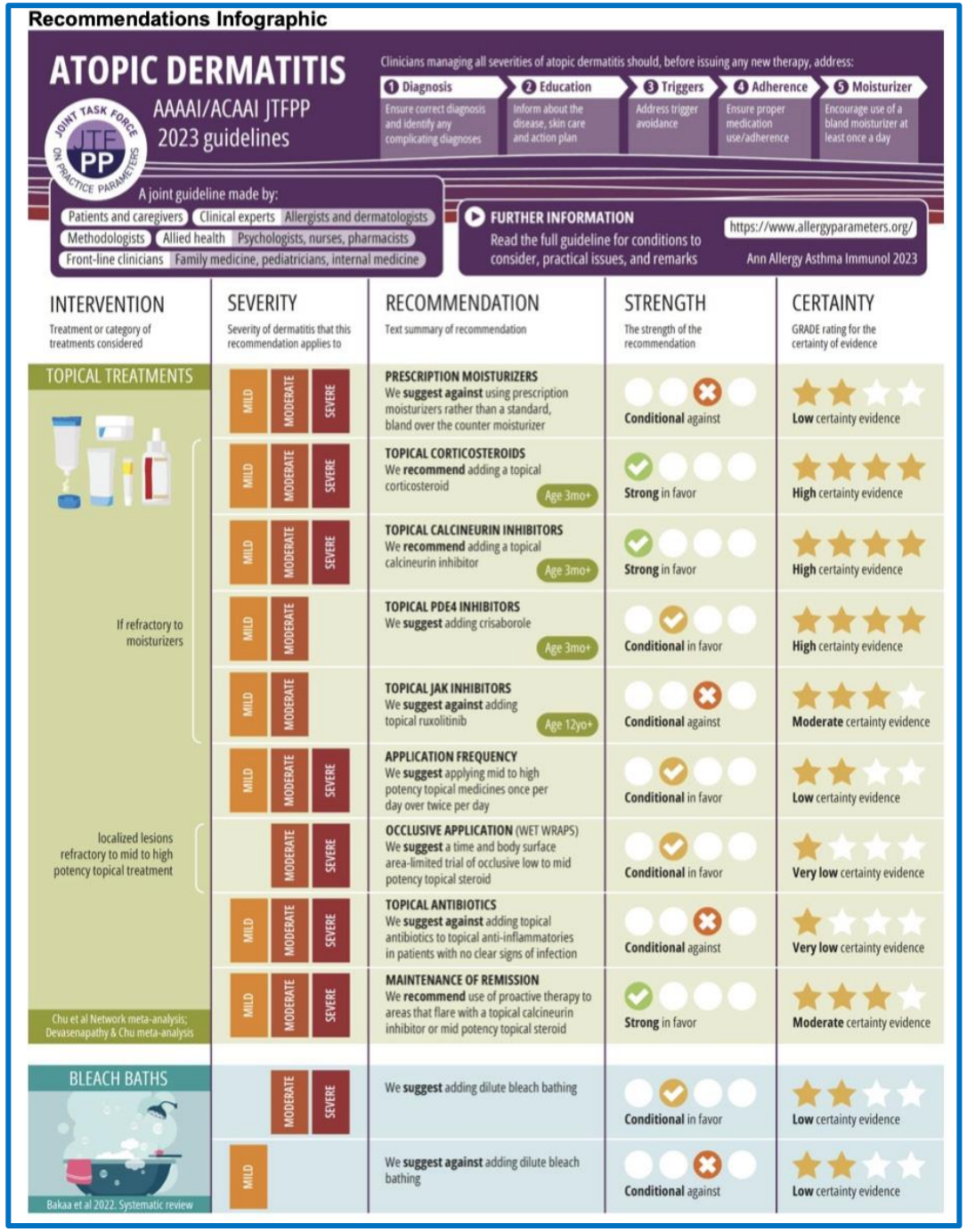
J Allergy Clin Immunol 2023; 152:1470

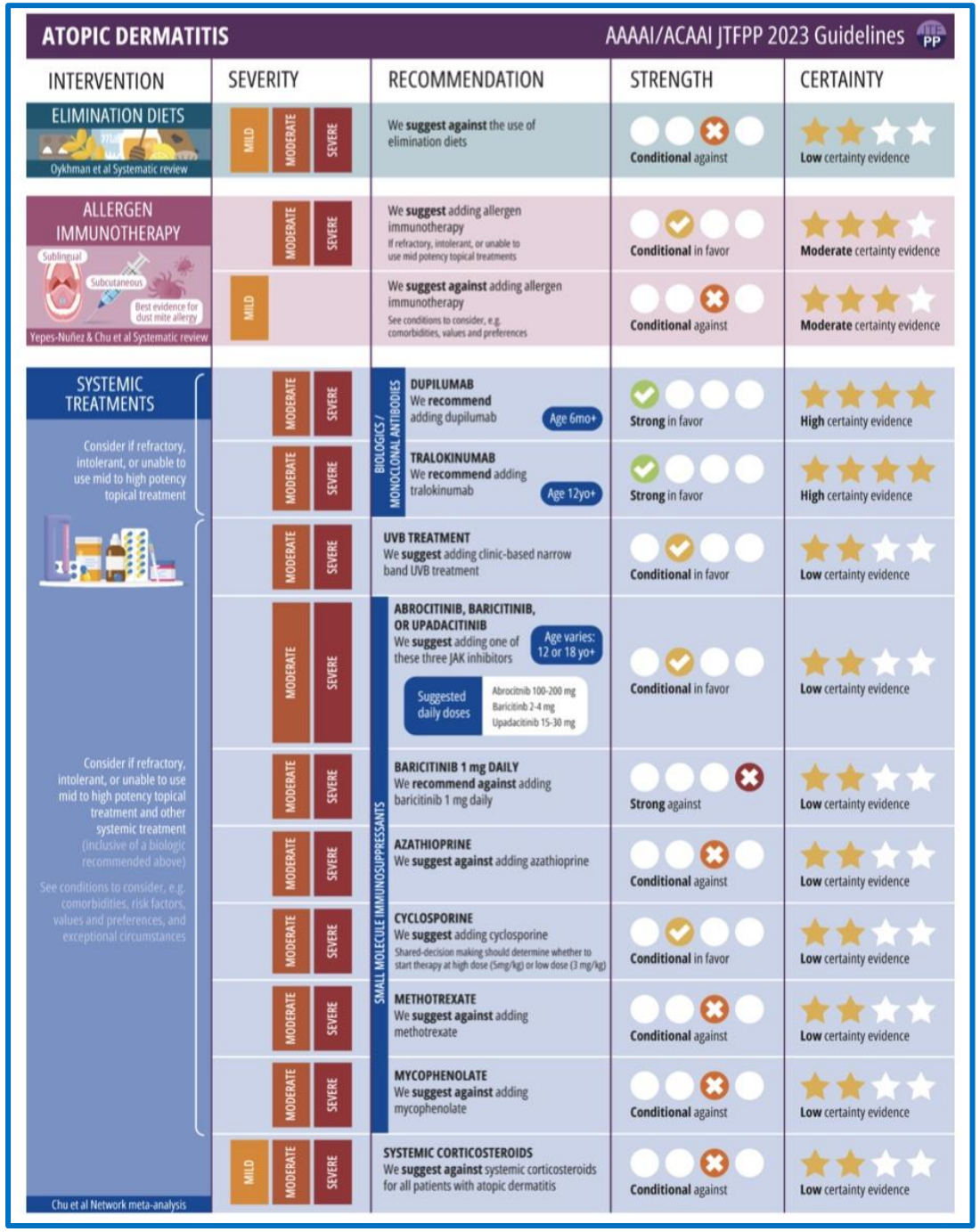
Atopic Dermatitis (eczema) guidelines: 2023 AAAAI/ACAAI Joint Task Force on Practice Parameters GRADE- and Institute of Medicine-based recommendations

- Panel agreed on 25 treatment recommendations to gain and maintain control of AD for patients with mild, moderate, and severe AD
- Strong recommendations:
  - Adding TCS and/or TCI for pts refractory to moisturization alone, and, after initial control of AD is achieved, addressing relapsing disease with continued intermittent (proactive) therapy
  - **In pts with moderate-to-severe disease refractory to this, panel recommended adding dupilumab or tralokinumab**
- Conditional recommendations:
  - Applying mid-potency topical agents once rather than twice daily, wet wrap therapy or crisaborole if aligned with patient values and preferences, not starting with topical JAK inhibitors as first-line therapy, and, depending on disease severity, adding bleach baths and allergen immunotherapy but not dietary avoidance nor systemic corticosteroids
  - Among pts refractory to topicals and biologics, panel provided multiple conditions to consider for optimal treatment selection, including oral JAK inhibitors, CsA or UV light

No discussion of PT prior to use of systemic therapies

Ann Allergy Asthma Immunol 2024;132:274





Ann Allergy Asthma Immunol 2024;132:274

ARTICLE IN PRESS

FROM THE ACADEMY

Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies

Dawn M. R. Davis, MD (Co-Chair),[a] Aaron M. Drucker, MD, ScM,[b,c] Ali Alikhan, MD,[d] Lionel Bercovitch, MD,[e] David E. Cohen, MD, MPH,[f] Jennifer M. Darr, LCSW,[g] Lawrence F. Eichenfield, MD,[h] Lindsy Frazer-Green, PhD,[i] Amy S. Paller, MD,[j] Kathryn Schwarzenberger, MD,[k] Jonathan I. Silverberg, MD, PhD, MPH,[l] Anne Marie Singh, MD,[m] Peggy A. Wu, MD, MPH,[n] and Robert Sidbury, MD, MPH (Co-Chair)[o]

J Am Acad Dermatol 2023;Nov 3:Online ahead of print

Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies

- Searching for “patch testing” = 0
- “When AD is refractory to standard treatments, including topical therapy and systemic therapies, alternate diagnoses such as allergic contact dermatitis and cutaneous lymphoma should be considered.”

J Am Acad Dermatol 2023

Patch Testing: An Underutilized Modality in the Dermatology World

- “Most dermatologists use patch testing infrequently, and a significant minority of dermatologists do not patch test at all”
- A recent study estimated that nearly 1 of 5 dermatologists do not perform patch testing at all
- Approximately 74% of dermatologists performing patch testing use the TRUE test
- Approximately 83% of dermatologists who do patch testing indicate that they perform testing on fewer than 5 patients each month
- Therefore, it is clear that most dermatologists perform very limited patch testing on a small number of patients
- It is important to determine relevance of positive patch test reactions:
  - One study on nickel allergy estimated that approximately 20% of 1+ positive reactions are relevant
  - The practicing dermatologist must clearly take enough time to review positive patch test findings and correlate findings with patient’s history to determine if tests are indeed relevant

Scheman A. Arch Dermatol 2004;140:1529

Prevalence of patch testing and methodology of dermatologists in the US: results of a cross-sectional survey

- Majority of patch testing dermatologists (52%) used a 48-hour, 96-hour patch test reading schedule, 26% performed a single reading at 48 or 72 hours
- Among patch testing dermatologists, most (74%) used TRUE Test

Am J Contact Dermat 2002;13:53

Clinically relevant limitations even with expanded PT

- Although many dermatologists and allergists use a standard panel (eg, North American Contact Dermatitis Group panel of 70 antigens or TRUE Test containing 35 antigens), as many as 25% of the patients are sensitized to clinically relevant allergens not included in a standard antigen panel
  - Warshaw EM, Belsito DV, Taylor JS, et al. North American Contact Dermatitis Group patch test results: 2009 to 2010. Dermatitis 2013;24:50-9

Practical issues with patch testing

- T.R.U.E. Test currently the only FDA approved PT for pts 6 yrs and older (35 antigens & 1 negative control)
- “Usefulness of PT enhanced with the number of allergens tested”
- “Allergens not found on commercially available screening series in the US frequently give relevant reactions”
- “Hypothetical detection rate of TT vs NACDG: 57.9-70.4%”
- “T.R.U.E. Test misses: 50% Fragrance, 62% Balsam of Peru, 56% Thiuram”
- Reimbursement (TRUE Test ~$140/set 36 Ag @~5.37/Ag=~$193)

T.R.U.E. TEST® (36) vs. NACDG Screening Series

Antigens in top NACDG not on TT®

- **methylisothiazolinone**
- **fragrance mix II**
- **benzisothiazolinone**
- **hydroperoxides of linalool**
- **propolis**
- carmine
- decyl glucoside
- majantol
- ammonium persulfate
- sodium metabisulfite
- dimethylaminopropylamine
- shellac
- hydroxyethylmethacrylate
- iodopropynyl butylcarbamate
- propylene glycol
- oleamidopropyldimethylamine
- DMDM hydantoin
- lauryl glucoside
- ylang-ylang oil

Other important non-TT® allergens

- **tosylamide formaldehyde resin**
- amidoamine
- **acrylates/methylacrylates**
- tea tree oil
- benzophenone-3
- mixed dialkyl thioureas
- **cocamidopropyl betaine**

Allergen panels developed based on recommendations from North American Contact Dermatitis (NACD) panel & American Contact Dermatitis Society (ACDS)

- Updated regularly to include most relevant allergens

NYU Langone Health

DeKoven et al. NACDG Patch Test Results:2017–2018 March 2021.DERMATITIS

NYU Long Island School of Medicine

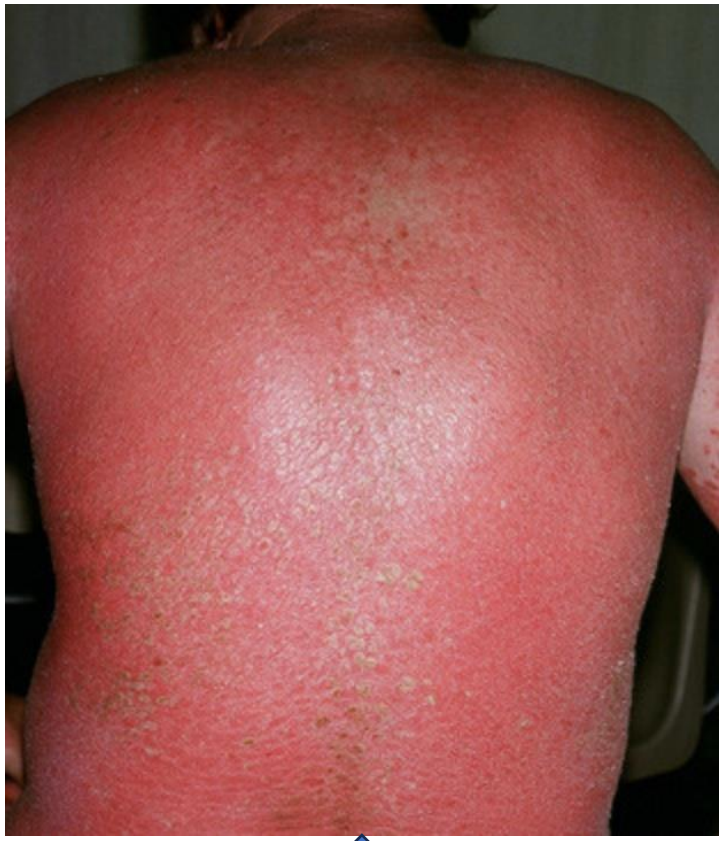
Fonacier L. AAAAI 2022

More practical issues with patch testing

- Practical pearls re sublties of interpretation: TNTC!
  - Who NOT to PT includes back involved, hirsute, covered in tattoos, on systemic steroids, UV exposure,...
  - False negatives & false positives especially problematic with AD: Angry back,...
- Need to attend one of Dr Fonacier's excellent PT workshops, and even then PT is not a "See one, do one..." experience!
- Cost vs reimbursement (TRUE Test ~$140/set 36 Ag,~$5.37/Ag=~$193)

Clinical dilemma

- A commonly encountered clinical situation is the patient with active, often severe, dermatitis on the back and other potential sites of application for the patch tests
- Patch testing on actively inflamed skin may lead to both false positive and false negative reactions
- Patient may also experience immense discomfort secondary to pruritus and pain from adhesives used, increased heat and sweat and exposure to potentially irritating reagents being tested
- “angry back syndrome” has been used to describe when patients develop positive reactions to most or all allergens tested



Patch test or biopsy?

Owen JL, et al. Am J Clin Dermatol 2018;19:293

From the T.R.U.E. Test reference manual...

- T.R.U.E. TEST product will be delivered with an expiration date of 8 months or longer
- Refrigerate T.R.U.E. TEST promptly after arrival. Do not freeze
- If T.R.U.E. TEST is not refrigerated for 4 hours or more, the product should be discarded
- Stability of T.R.U.E. TEST allergens is temperature dependent. Users can minimize product deterioration and optimize performance by adhering to recommended temperature limits. When stored between 36 - 46 F, T.R.U.E. TEST shown to maintain its allergen concentration at +20% of batch release levels. When stored at higher temperatures, T.R.U.E. TEST allergens have been shown to deteriorate
- Expired T.R.U.E. TEST product cannot be returned

A Pragmatic Approach to Patch Testing Atopic Dermatitis Patients: Clinical Recommendations Based on Expert Consensus Opinion...

Jennifer K. Chen, MD, Sharon E. Jacob, MD, Susan T. Nedorost, MD, Jon M. Hanifin, MD, Eric L. Simpson, MD, MCR, Mark Boguniewicz, MD, Kalman L. Watsky, MD, Aida Lugo-Somolinos, MD, Carsten R. Hamann, MD, Cheryl Lee Eberting, MD, Jonathan I. Silverberg, MD, PhD, MPH, and Jacob P. Thyssen, MD, PhD

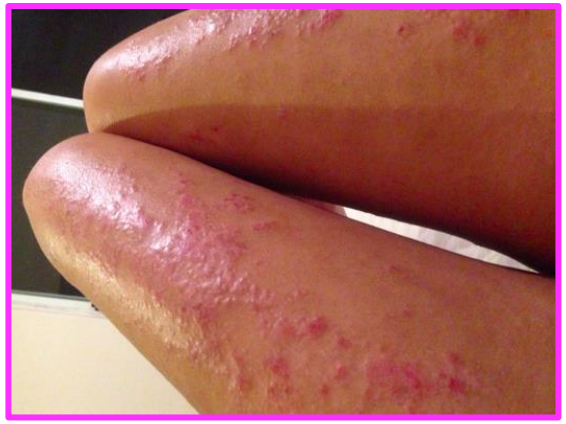
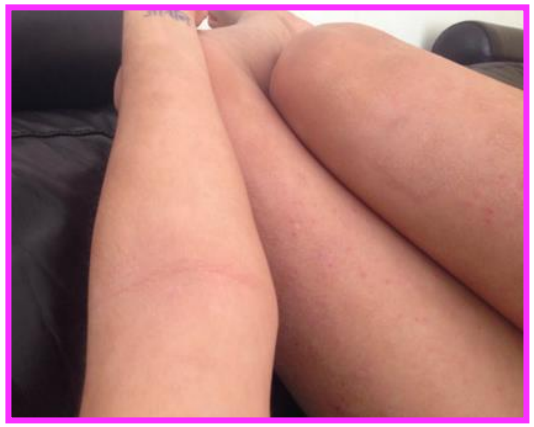
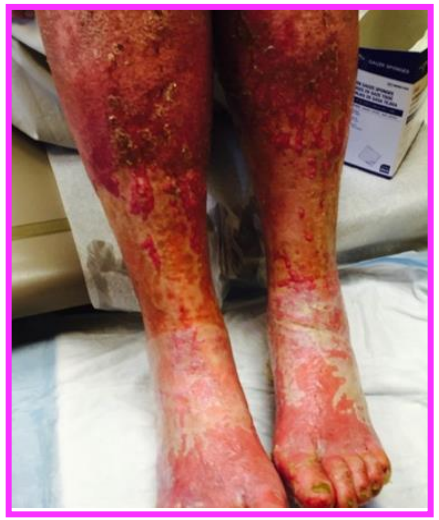
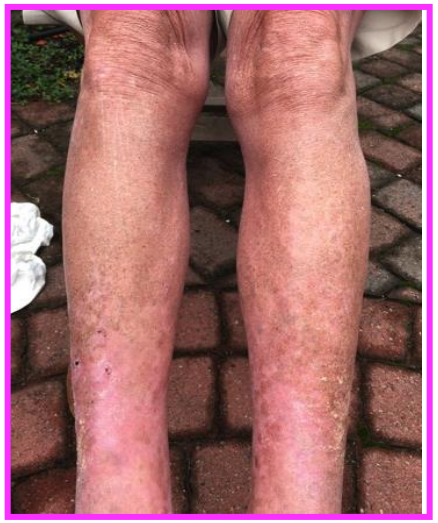
- "Patch testing should be considered in AD patients with dermatitis that fails to improve with topical therapy; with atypical/changing distribution of dermatitis, or pattern suggestive of ACD; with therapy-resistant hand eczema in the working population; with adult- or adolescent-onset AD; and/or before initiating systemic immunosuppressants for the treatment of dermatitis"

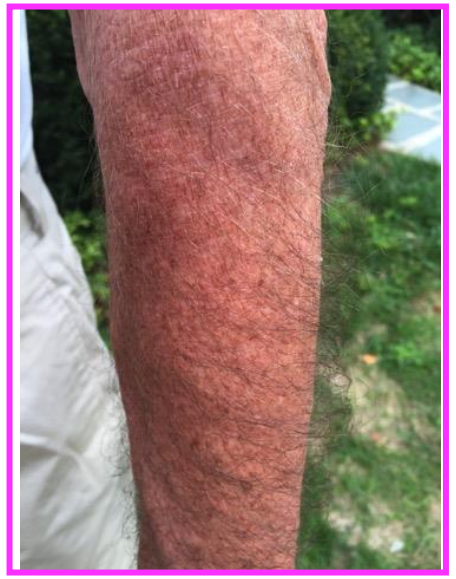
Dermatitis 2016;27:186

In conclusion...

- PT makes sense for some pts with AD...history may point to which may be at greatest risk for having ACD complicating their AD (e.g. recalcitrant facial, hand/foot worsening with TCS, etc)
- PT an imperfect science...best left to those with expertise and there are not enough of them to make it practical prior to starting every patient suffering from AD to wait for appointment, have a clear back, be off of contraindicated meds, be tested to the relevant antigens (!) ...
- Enough roadblocks already put up for busy clinicians trying to help patients...lets not complicate matters any more as we try to help our moderate-to-severe AD patients
- Can always re-visit PT depending on response to a systemic therapy, especially if risk:benefit of e.g. a biologic favors benefit

AD patients from phase 2 & 3 trials pre-/post-dupilumab



Boguniewicz M, **Fonacier L**, et al. Ann Allergy Clin Immunol 2018;120:10