Article Type: From the Academy

Title: Guidelines for diagnostic testing in adults with presumed atopic dermatitis refractory to treatment

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Funding sources: This study was funded in total by internal funds from the American Academy of Dermatology.

Conflicts of Interest: Listed in text following references.

Supplementary files are available on: [Insert Mendeley data URL]
Reprint Requests: No reprints available.

Manuscript word count: words [excluding abstract, references, figures, tables, appendix]
Abstract word count: 168
References:

Figures:
Online Supplementary figures:

Keywords: atopic dermatitis, differential diagnosis, diagnostic testing, patch testing, skin biopsy, skin scraping

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Abstract

Background: While many adults diagnosed with atopic dermatitis (AD) achieve disease control with standard treatments, a subset of patients remain refractory to optimal management. In these cases, misdiagnosis or the presence of concomitant conditions may be contributing to treatment failure.

Objective: To provide evidence-informed guidance for the diagnostic workup of presumed adult AD unresponsive to optimized treatment.

Methods: An expert multidisciplinary workgroup applied GRADE methodology for issuing guidance on approaching suspected AD refractory to treatment by reviewing the indirect evidence, assessing the balance of benefits and harms, and reaching consensus.

Results: The workgroup developed a Good Practice Statement on the diagnostic workup of adults with presumed AD unresponsive to therapy.

Limitations: This guidance is based on indirect evidence and expert consensus, as direct empirical data on diagnostic workup strategies for treatment-resistant AD are lacking. Applicability may vary depending on access to dermatologic and allergy specialist care.

Conclusion: The Good Practice Statement supports consideration of diagnostic reassessment in cases of presumed AD in adults not responding to optimized treatment.

Abbreviations

AD: atopic dermatitis

ACD: allergic contact dermatitis

CTCL: cutaneous T-cell lymphoma

GPS: Good Practice Statement

GRADE: Grading of Recommendations, Assessment, Development, and Evaluation

JAK: Janus kinase

TCS: topical corticosteroid

Scope & Objectives

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease marked by immune dysregulation and skin barrier dysfunction, frequently affecting individuals with a genetic predisposition.[2, 3] While AD most often begins during childhood, the condition can present *de novo* in adulthood or recur as a continuation of childhood-onset disease. The worldwide prevalence of AD in adults is 2.0%, with 25% of adults with AD reporting adult-onset.[4, 5]

While some patients diagnosed with AD achieve disease control with standard topical or systemic therapies, a subset of individuals experience persistent symptoms despite optimal treatment following guideline recommendations and patient adherence, raising diagnostic uncertainty and the possibility of alternative or coexisting cutaneous or systemic disease.[6-10] AD may be misdiagnosed or mask comorbid skin conditions in more than 20% of adults with refractory AD prescribed a systemic medication.[11] In cases of suboptimal therapeutic response, diagnostic reassessment can identify alternative or concomitant conditions, such as allergic contact dermatitis (ACD), drug eruptions, tinea, cutaneous T-cell lymphoma (CTCL), psoriasis, or scabies, that may alter the therapeutic approach.

This guideline aims to support diagnostic clinical decision-making in refractory adult AD to improve patient outcomes.

Diagnosis of Adult AD

Diagnosis of adult-onset or recurrent AD in adults can be challenging. There can be differences in lesional distribution, morphology, associated signs, and comorbidities compared to the more common childhood-onset AD, and clinical features may significantly overlap with those of other conditions.[4, 12-14] As there is no single defining test or feature, the diagnosis of AD in adults is primarily clinical, based on a history and physical examination per established diagnostic criteria (**Box 1**). However, the pediatric origins of standard AD diagnostic criteria, such as those by Hanifin and Rajka or the UK Working Party, may limit their applicability in adults.[15]

A few atopic or immune-mediated conditions are associated with AD in adults with high or moderate certainty evidence, and when combined with the clinical presentation, may help support a diagnosis AD. These include asthma, food allergies, allergic rhinitis, alopecia areata, and urticaria.[16]

The diagnostic process relies on clinical evaluation, including a history of pruritus, relapsing eczematous lesions, and personal or family history of atopy. Characteristic physical signs include erythema, edema, xerosis, lichenification, oozing and crusting, and involvement of the hands, face, neck, and flexures.[1] The appearance of erythema can be

altered in patients with darker skin, and in addition to a red or pink color, sites of active skin inflammation can manifest as shades of purple, gray, or brown. AD lesions in patients with darker skin may be more likely to be lichenified, papular, and present in extensor regions. Changes in pigmentation (hyper- or hypopigmentation) following skin inflammation can be prominent and long-lasting in all skin types, and particularly in patients with darker skin.[17]

In addition to classic eczematous lesions of AD, adults may present with nummular or prurigo-like lesions, cheilitis, may lack Dennie-Morgan lines, and have lower rates of flexural involvement.[1, 15, 18-20] Additionally, a personal or family history of atopy is less common in adult-onset AD.[13] As a group, adults generally have more comorbidities, some requiring medications; the incidence of other papulosquamous diseases, infection, autoimmune phenomena, and skin malignancy also increases with age.[21-24] A key consideration with adult-onset AD is the wide-ranging differential diagnosis, including ACD, psoriasis, drug eruptions, and CTCL, which can have overlapping clinical features.[18]

Box 1. Features to be considered in the diagnosis of patients with atopic dermatitis

Adapted with permission from the American Academy of Dermatology from Eichenfield 2014[1]

ESSENTIAL FEATURES—Must be present:

- Pruritus
- Eczema (acute, subacute, chronic)
    - Typical morphology and age-specific patterns*
    - Chronic or relapsing history

*<u>*Patterns include:*</u>

1. *Facial, neck, and extensor involvement in infants and children*
2. *Current or previous flexural lesions in any age group*
3. *Sparing of the groin and axillary regions*

IMPORTANT FEATURES—Seen in most cases, adding support to the diagnosis:

- Early age of onset
- Atopy
    - Personal and/or family history
    - Immunoglobulin E reactivity
- Xerosis

ASSOCIATED FEATURES—These clinical associations help to suggest the diagnosis of atopic dermatitis but are too nonspecific to be used for defining or detecting atopic dermatitis for research and epidemiologic studies:

- Atypical vascular responses (eg, facial pallor, white dermographism, delayed blanch response)
- Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
- Ocular/periorbital changes
- Other regional findings (eg, perioral changes/periauricular lesions)
- Perifollicular accentuation/lichenification/prurigo lesions

EXCLUSIONARY CONDITIONS—It should be noted that a diagnosis of atopic dermatitis depends on excluding conditions such as (in alphabetical order):

- Connective tissue disease
- Contact dermatitis (irritant or allergic)
- Cutaneous T-cell lymphoma
- Erythroderma of other causes
- Ichthyoses
- Immune deficiency diseases
- Photosensitivity dermatoses
- Psoriasis
- Scabies
- Seborrheic dermatitis
- Tinea corporis

Methods

The multidisciplinary guideline workgroup followed the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to assess the certainty of evidence and formulate recommendations.[25] A scoping search of the literature was originally conducted in July 2024 and updated in April 2025 to identify direct, relevant evidence regarding the need for further diagnostic workup in adults with suspected AD that is unresponsive to optimal AD management. This search did not identify any direct evidence addressing this specific clinical scenario. See **Supplemental Table 1** for an overview and summary of the identified indirect evidence.

In the absence of direct evidence, the guideline workgroup issued the following Good Practice Statement (GPS):

> **For adults with suspected AD that is unresponsive to AD management, we recommend considering further workup (Good Practice Statement)**

The GPS follows the principles outlined in the GRADE framework (**Table II**).[26, 27] A GPS is supported by indirect evidence and clinical consensus and is warranted when an action has an overwhelmingly clear benefit-to-risk balance.

The workgroup agreed that failure to conduct further diagnostic workup in such cases could lead to missed alternative diagnoses, inappropriate treatment, or delayed management of other underlying conditions. Given these considerations, the workgroup concluded that further evaluation is warranted in cases where AD remains unresponsive to guidelines-recommended, optimized management.

Table II. GRADE standards for developing a good practice statement

GRADE GPS Criterion[26]	Rationale
1.Is the statement clear and actionable?	Yes, the recommendation provides clear guidance: clinicians should consider further diagnostic workup when a patient does not respond to optimized AD treatment. It does not prescribe a specific test but suggests an individualized approach based on clinical presentation.
2. Is the message necessary in regards to health practice?	Yes. If an individual's skin condition is not improving with standard AD treatment, failing to conduct further workup could result in misdiagnosis, delayed diagnosis of serious conditions, and/or unnecessary exposure to ineffective or harmful treatments.
3.Will implementing the GPS result in large net positive consequences?	Yes. The benefit of confirming an accurate diagnosis is substantial, as it allows for targeted treatment. There is no reasonable doubt that further workup can prevent prolonged suffering, inappropriate treatment, or complications from undiagnosed conditions.
4. Is collecting and summarizing the evidence a poor use of limited resources?	Yes. Indirect evidence and standard clinical and diagnostic reasoning overwhelmingly support the need for further evaluation in unresponsive cases. The time and effort required to conduct a formal review of the abundant indirect evidence would not add meaningful value to decision-making.

5. Is there a well-document clear and explicit rationale connecting the indirect evidence?	Yes. Indirect evidence from varied disease states and fields of medicine and case-based data in presumed AD supports re-evaluation of treatment-unresponsive presentations and confirms that misdiagnosis can lead to inappropriate and ineffective care. This aligns with fundamental principles of clinical logic and diagnostic reasoning, and harm avoidance from misdiagnosis.

Clinical considerations for further workup

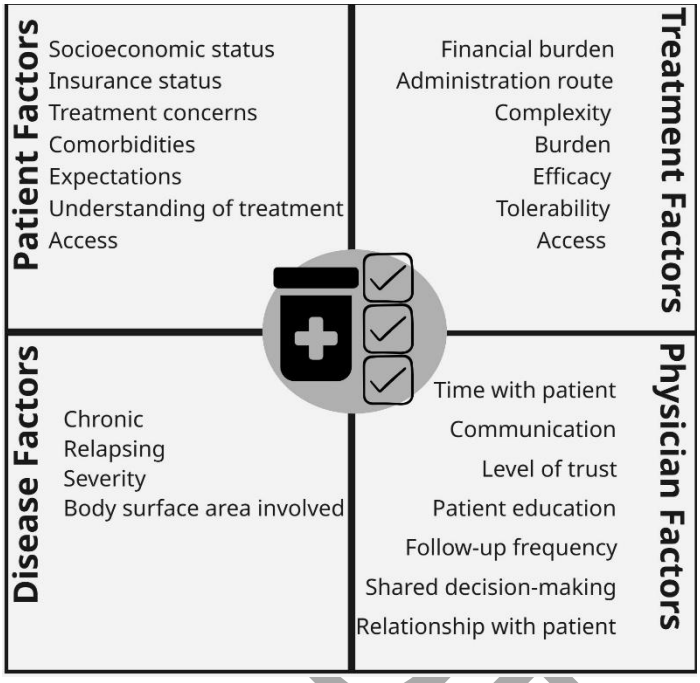
AD management

Guidelines-recommended, optimized AD management and patient adherence to therapeutic strategies should be confirmed before considering additional diagnostic workup due to non-response to AD therapy. A stepwise, individualized approach based on disease severity and patient factors like comorbidities and preferences is required for optimized treatment of AD.

Foundational treatment across disease severities includes non-pharmacologic interventions, such as emollient use and trigger and allergen avoidance.[28] Treatment of mild-to-moderate AD generally includes topical anti-inflammatory agents like low to mid-potency topical corticosteroids (TCS), topical calcineurin inhibitors, topical phosphodiesterase inhibitors, topical aryl hydrocarbon receptor agonists, or topical JAK inhibitors.[28] Phototherapy may also be considered for the management of mild-to-moderate disease not adequately controlled with topical therapy.[29] Unresponsive disease may require mid- to high-potency TCS.[28, 29] Proactive treatment using topical anti-inflammatory agents is also recommended to reduce flares in moderate and recurrent AD.[28] Moderate-to-severe AD may necessitate the use of biologics, JAK inhibitors, or systemic immunomodulatory agents such as cyclosporine and methotrexate, to achieve adequate disease control in addition to topical and/or phototherapy.[29]

Patient adherence with AD management strategies should also be considered when assessing suboptimal therapeutic outcomes. Patient-, treatment-, physician-, and disease-centered factors influencing adherence include access, socioeconomic status, treatment complexity, route of administration, and burden, fear of adverse events, physician and patient relationship, and treatment fatigue caused by the chronic, relapsing nature of AD (**Figure 1**).[30-33] A prominent barrier to adherence in AD management is "steroid phobia," or disproportionate concern of potential adverse events of TCS use, such as skin atrophy and systemic absorption.[34, 35 36, 37] Adherence is key to optimal management of AD and requires scrutiny before considering confounding dermatoses or misdiagnosis in adults with presumed AD refractory to therapy.

Figure 1. Atopic dermatitis treatment adherence factors



Treatment-refractory AD

Treatment failure in AD has been characterized as disease that does not respond adequately to treatment despite adherence to optimally prescribed therapies.[38-40] This may apply to topical or systemic therapies. As there are no universal standards or timelines for the assessment of treatment response or non-response in AD, treatment failure is typically assessed within a defined period, based on the treatment's expected onset of action.[41]

Timing of assessments and follow up

There is no universal consensus amongst experts or in the literature on pre-management workup for AD or optimal follow-up time frames. Given the estimated overlap between concomitant allergic contact dermatitis (ACD) and AD, ranging from 7 to 91%, some authors recommend evaluation for ACD before starting systemic AD therapy.[42] In addition to consideration of patch testing, other groups have suggested ruling out skin infections, specialist referral, and other diagnostic considerations prior to starting systemic AD therapy or escalation of care. [43-45]

A range of follow-up time frames was reported in the literature with some authors assessing every 4 to 8 weeks in the first 3 months of systemic therapy.[46] In our systematic review of the literature on AD misdiagnosis or confounding diagnoses, the delay in best management was a median of 6 months (range 3 to 12 months) for ACD (**Supplemental Table 2**). The median delay for CTCL was 24 months (range 8 to 144 months), and within

that subset, the median duration of time on systemic therapy for presumed AD was 6 months (range 1 to 96 months). The average delays for best management for other infectious or inflammatory diseases, such as scabies, pityriasis rubra pilaris, familial benign pemphigus, were around 19.5 months, and for autoimmune conditions, 90 months.

Confounding dermatoses

When optimized AD management and patient adherence have been assessed and addressed in presumed adult AD, but the disease remains refractory to therapy, further diagnostic workup should be considered. Several medical conditions clinically resemble or occur concomitantly with AD and should be considered in the differential diagnosis for treatment-refractory presumed AD (**Supplemental Tables 3-4**). These include allergic or irritant contact dermatitis, autoimmune diseases, bacterial, viral, or fungal skin infections, malignancies, and infestations. **Table III** summarizes the clinical and diagnostic features for some alternative or concomitant diagnoses to consider in treatment-resistant suspected adult AD.

Table III. Clinical and diagnostic factors to consider in the further workup of treatment-resistant presumed adult atopic dermatitis.

Differential Diagnosis	Clinical Features	Primary Diagnostic Testing	Testing Considerations
Allergic/irritant contact dermatitis (ACD/ICD)	Localized or widespread eczematous rash, especially on head/neck or hands/feet; often well-demarcated; development of signs outside of previously affected areas; inability to manage disease on established skin regimen; exposure history Systemic Contact Dermatitis is a type VI hypersensitivity (ACD) reaction following systemic absorption of an allergen (eg, ingestion, intraveneous, subcutaneous) and can present in a myriad of ways including but	Patch testing for ACD and determine relevance of reactions.	Consider expanded series patch testing battery. Consider systemic, environmental, and occupational exposures

	not limited to generalized, intertriginous, vesicular hand dermatitis distributions		
Autoimmune blistering diseases (e.g., dermatitis herpetiformis, bullous pemphigoid)	Bullae or vesicles on skin/mucous membranes Systemic manifestations	Skin biopsies for histopathology and direct immunofluorescence	
Bacterial skin infection (e.g., impetigo, ecthyma, folliculitis)	Crusted erosions, honey-colored crusts; localized or diffuse; follicular pustules (folliculitis)	Bacterial skin culture	AD is commonly colonized by s. aureus; Secondary infection may complicate AD, but a positive culture does not always imply infection
Cutaneous lupus erythematosus	Photosensitivity, skin discoloration, red scaly rash	Skin biopsy	
Cutaneous T-cell lymphoma/mycosis fungoides/Sezary syndrome	Adult-onset with atypical features Persistent despite topical therapy; raised plaques, nodules, ulcers Lymphadenopathy Systemic manifestations	Skin biopsy (ies)*	*Multiple biopsies may be needed and/or additional immunohistochemical or clonality studies. If initial biopsies are inconclusive, consider additional biopsies over time or a change in disease morphology
Drug eruptions	Sudden onset, no flexural involvement, blisters, pustules, sensitivity to sunlight, lack of pruritus	Skin biopsy; patch test	
Fungal skin infection (e.g., candidiasis, dermatophytes: tinea corportis) Tinea incognito	Dermatitis in intertriginous areas or feet Annular, scaly borders Non-responsive to TCS Annular lesions with central clearing, raised borders Initial improvement, then worsening with steroid use. Annular or asymmetric lesions extend beyond typical eczematous distributions	Skin scraping with microscopy; fungal culture; skin biopsy Skin scraping for microscopy; fungal culture; skin biopsy	

Nutritional deficiencies (e.g. deficiencies of iron, zinc, biotin and other vitamins)	Glossitis, arthralgias, diarrhea, anemia, neurologic deficits, perioral dermatitis & angular cheilitis (zinc deficiency), phrynoderma, nail changes, hyperpigmentation	Skin biopsy	
Pityriasis rubra pilaris (Type I or Type II)	Scalp erythema Papules Eczematous plaques "Islands of sparing" Ichthyosiform scale	Skin biopsy(ies)*	*Multiple biopsies may be needed.
Psoriasis	Lack of pruritus and oozing or crusting	Skin biopsy	
Prurigo nodularis	Nodular lesions, extensor surface involvement, no facial invovlment	Skin biopsy	
Scabies (esp. Norwegian/crusted)	Acute onset Burrows, inguinal, axillary, genital papules, severe pruritus (worse at night), involvement of hands, genitalia Close contacts with itchy rash Often in elderly/care home residents	Skin scraping with microscopy; skin biopsy	
Viral Skin Infection (e.g., eczema herpeticum, eczema coxsackium)	Acute onset, grouped vesicles on erythematous base; punched-out erosions; fever possible	Viral culture or viral polymerase chain reaction	

Specific diagnostic testing considerations

When adults present with recalcitrant or atypical dermatitis presumed to be AD, consideration of a broad diagnostic approach incorporating patient-reported symptoms, medical personal and family history, comorbidities, comprehensive skin exam findings, as well as serologic, molecular, photobiologic, microbiologic, and allergy testing, in conjunction with clinical judgment, is suggested to address misdiagnoses and ensure appropriate management.

Patch Testing

Allergic or irritant contact dermatitis can resemble or coexist with AD, particularly in adults with new-onset or treatment resistance.[42, 47] Patch testing is the gold standard for

identifying hypersensitivity reactions to contact allergens, and comprehensive patch testing should be considered in adult patients who present with adult-onset dermatitis with atypical distribution of lesions (e.g., hands, face, eyelids), chronic relapsing dermatitis unresponsive to or worsening despite standard AD therapy, or new or worsening facial dermatitis.[7, 48-59]

Patch testing can identify concomitant ACD in AD. The co-occurrence of these conditions leading to difficult-to-treat AD is increasingly documented due to skin barrier alterations, and the use of emollients, topical medications, personal care products, and occupational exposures in this population.[6, 60-63] Distinguishing between these entities or identifying concomitant ACD is essential to addressing treatment-refractory AD, as the management of these conditions differs significantly. AD often requires immunomodulation, whereas ACD requires allergen avoidance.

An expanded patch-testing battery that accounts for pertinent environmental and occupational exposures is suggested.[42] Testing should be considered with the presentation noted above ideally before the initiation of systemic therapy for AD.[42, 60] If ACD is suspected, patch testing may also be performed while on AD therapies, potentially with some adjustment of dose or timing.[64] Depending on the results and clinical course, patch testing may also warrant repeating.

Skin biopsy

A skin biopsy, such as a punch biopsy, with hematoxylin and eosin staining and potential addition of special stains (for infection, immunohistochemistry, etc.), clonality studies as indicated, or direct immunofluorescence can distinguish presumed AD from other cutaneous, autoimmune, malignant, or inflammatory conditions, including pityriasis rubra pilaris, bullous pemphigoid, dermatitis, cutaneous lupus, or CTCL, particularly mycosis fungoides.[65-75] As the histopathologic features of inflammatory skin disease and other diagnoses such as CTCL can be subtle and complex, the pathologic evaluation of these cases may call for specialized training in dermatopathology to ensure diagnostic accuracy.

One or more skin biopsies may be indicated with a presentation of plaques, patches, papules, and tumors, or a diffuse or generalized pruritic erythema (erythroderma) and enlarged lymph nodes, or other systemic symptoms as this is the commonly described clinical phenotype for CTCL, specifically mycosis fungoides, in adults with refractory AD later determined to be CTCL.[69, 72, 76-80] In some cases, especially with suspected CTCL, more than one biopsy and reassessment over time may be needed to be diagnostic (**Supplemental Table 5**). A change in skin morphology to the development of blisters can precede some autoimmune manifestations of bullous disease and lead to biopsy

consideration (**Supplemental Table 6**).[66, 67] The range of biopsies needed in the literature of misdiagnosis in refractory adult presumed AD to confirm an alternative diagnosis was 1-4 (median 2 biopsies).[66-72, 78-92]

Skin scraping

Skin scraping with microscopy using potassium hydroxide preparation or mineral oil, or fungal or bacterial culture facilitate accurate identification of infestations and infections that clinically resemble or complicate AD, such as scabies or tinea, ensuring targeted treatment and preventing the inappropriate use of topical corticosteroids and topical immunomodulators, which can exacerbate the underlying conditions.[65, 93-96]

The most common alternative diagnosis in the literature identified by skin scraping is scabies, a parasitic infestation that can closely resemble AD due to its intense pruritus, excoriated papules, and widespread distribution.[93-96] Misdiagnosis as AD often leads to inappropriate treatment with topical steroids, which can worsen infestation.[94, 95] Microscopic examination of skin scrapings, obtained from burrows or papules, can reveal mites, eggs, or fecal pellets, confirming the diagnosis.[97, 98]

Additionally, skin scrapings with potassium hydroxide or fungal culture, or skin swabs for fungal culture can identify dermatophyte infections like tinea corporis or tinea incognito and Malassezia-associated dermatoses, which may be mistaken for or occur concomitantly with AD, particularly when steroid use masks classic features.[65, 99-103] Tinea incognito, in particular, is a fungal infection altered by steroid or other immunomodulatory medication use, leading to an atypical presentation.[99, 100, 104, 105] Lesions often lack the typical annular appearance and may appear more eczematous, lichenified, or psoriasiform, or have a purpuric or vesicular appearance.[105 106] Heightened clinical suspicion is warranted in cases of presumed AD that initially improve but ultimately fail to respond to or worsen with steroids or other topical treatments, particularly when lesions appear annular, asymmetric, or extend beyond typical eczematous distributions.[104, 105] Early identification and treatment with appropriate antifungal agents are essential to prevent progression and recurrence.

Other diagnostic testing

Beyond patch testing, skin biopsy, and skin scraping, several other adjunctive diagnostic tests can aid in the differential diagnosis of presumed AD refractory to treatment.

Skin swabs for bacterial, viral, or fungal cultures may be warranted when infection is suspected with crusting, erythema with induration, oozing, vesicles, punched-out ulcers, or pustules. If superinfection with a virus, such as herpes simplex or varicella is suspected, if available, viral polymerase chain reaction testing may produce faster results. Skin swabs

for culture may show growth in the setting of colonization and results should be clinically correlated with the signs of infection noted above.

Photodermatoses such as chronic actinic dermatitis or photoallergic contact dermatitis may clinically resemble or occur concurrently with AD, especially in the setting of skin disease predominantly in a sun-exposed/photo-distributed pattern.[107] Phototesting with UVA/UVB exposures and photopatch testing can identify abnormal photosensitivity patterns and support a diagnosis of photodermatitis.

Laboratory studies like a complete blood count with differential, comprehensive metabolic panel, autoimmune serologies, peripheral blood flow cytometry or clonality studies, or other additional tests may be indicated in specific situations, such as with signs or symptoms of systemic disease or malignancy.

Access and feasibility considerations

Access to dermatology specialists, allergists, or specific diagnostic procedures can vary by healthcare setting. Performing further diagnostic workup in patients with refractory AD may be challenging in resource-limited settings where such testing is not readily available. In these contexts, clinicians may need to prioritize tests based on the most likely alternative diagnoses and consider specialist referral.

Specialist referral

Referral to a specialist for diagnostic considerations and workup is suggested when the clinical picture is unclear, initial diagnostics are inconclusive, or the suspected condition is high-risk.[108] Specialists bring advanced diagnostic capabilities, a deeper understanding of clinical-pathologic correlation, and access to additional resources such as expanded allergen panels and immunofluorescence studies. Timely referral not only improves diagnostic accuracy but also ensures appropriate treatment and minimizes unnecessary interventions or patient distress.[108]

Patch testing presents several feasibility challenges as it requires standardized allergen panels, trained personnel, and multiple patient visits for application and interpretation over 48 to 96 hours.[42, 60] Differentiating between irritant and allergic reactions, grading severity, and correlating results with the patient's history require experience and training.[42, 109]

The diagnostic utility of a skin biopsy is dependent on selecting the appropriate biopsy site and technique.[110] Referral to a dermatology specialist is advised for complex cases as dermatologists are trained in advanced techniques and the correlation of clinical patterns with histologic findings, particularly in conditions like autoimmune dermatoses, cutaneous malignancies, or atypical rashes.[108]

Skin scraping is one of the most accessible dermatologic diagnostic tools and can be performed effectively in most practice settings. However, diagnostic accuracy depends on adequate sampling and the ability to recognize fungal hyphae or mites microscopically.[111-113] Referral is recommended when scrapings are negative despite high clinical suspicion, when infections are widespread or recurrent, or when systemic treatment is being considered.[112, 113]

Limitations, Future Directions, and Research Priorities

Empirical data on optimal diagnostic strategies in presumed AD in adults non-responsive to therapy are limited. Research is needed to define and validate standardized diagnostic algorithms, as well as appropriate follow up times for this clinical population. This includes identifying clinical features or biomarkers that can reliably guide the selection of further tests. To develop high-yield diagnostic protocols and avoid unnecessary workup, studies evaluating the prevalence and types of conditions that clinically resemble or coexist with AD in patients who do not respond to standard treatments are needed. Randomized or well-designed observational studies comparing different diagnostic strategies would provide insight into whether additional diagnostic workup leads to improved patient outcomes.

Conclusion

For adults with suspected AD that is unresponsive to optimized, guideline-recommended AD management, we recommend considering further diagnostic workup. This recommendation is grounded in established clinical reasoning, abundance of indirect evidence, and consensus among experts. Diagnostic uncertainty, including the possibility of misdiagnosis or comorbid conditions, may be considered in treatment-refractory AD. In such cases, timely and appropriate diagnostic workup can lead to more effective management strategies and improve patient-important outcomes.

Implementation of this recommendation requires judicious clinical judgment. Decisions regarding further workup should be individualized, based on clinical features, and treatment optimization and adherence. Over-testing may increase healthcare costs, cause unnecessary patient burden, and result in diagnostic confusion, while under-testing may delay appropriate treatment and worsen outcomes. Until further empirical data become available, clinical expertise remains the cornerstone of appropriate decision-making in this context. Future research should focus on delineating high-yield diagnostic strategies, evaluating the impact of testing on clinical outcomes, and optimizing care pathways for this complex patient population.

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Work Group Members' Disclosures

The information below represents the authors' disclosed relationship with industry during guideline development. Authors (listed alphabetically) with relevant conflicts with respect to this guideline are noted with an asterisk*. In accordance with AAD policy, a minimum 51% of Work Group members did not have any relevant conflicts of interest.

Participation in one or more of the listed activities below constitutes a relevant conflict:

- service as a member of a speaker bureau, consultant, advisory board, for pharmaceutical companies on atopic dermatitis or atopic dermatitis drugs in development or FDA-approved.
- sponsored research funding or investigator-initiated studies with partial/full funding from pharmaceutical companies on atopic dermatitis or atopic dermatitis drugs in development or FDA-approved

If a potential conflict was noted, the work group member recused themselves from the discussion and drafting of recommendations pertinent to the topic area of interest. Complete group consensus was obtained for draft recommendations. Areas where complete consensus was not achieved are shown transparently in the guideline.

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of Pretel, Inc. and serves as a data safety monitoring board member for Pfizer, Inc. receiving fees. Robert Sidbury*, MD, MPH serves as an advisory board member for Pfizer, Inc. receiving honoraria; as a principal investigator for Regeneron receiving grants and research funding; as an investigator for Brickell Biotech, Inc., and Galderma USA receiving grants and research funding; as a consultant for Galderma Global and Microes receiving fees or no compensation. Jonathan I. Silverberg*, MD, PhD, MPH, serves as an advisory board member for BioMX, Boehringer Ingelheim, RAPT Therapeutics, Celgene, Ortho Dermatologics, TARGET Pharma, AFYX Therapeutics, Corrona, Inc., Dermira, Pfizer, Inc., Leo Pharma, Inc., and Menlo Therapeutics receiving honoraria and/or fees; as an investigator for DS Pharma, TARGET Pharma, Kiniksa Pharmaceuticals, Ltd., Menlo Therapeutics, GlaxoSmithKline, AbbVie, Leo Pharma, Inc., and Regeneron receiving research funding, honoraria, or no compensation; as a consultant for AOBiome, Bluefin Biomedicine, Bodewell, BiomX, Inc., Galderma Research & Development, LLC., Arena Pharmaceuticals, Dermavant Sciences, Incyte Corporation, DS Biopharma, Sun Pharmaceutical Industries, Ltd., AnaptysBio, Asana Biosciences, LLC., Pfizer, Inc., Glenmark Generics, Inc., Sanofi, Kiniksa Pharmaceuticals, Ltd., GlaxoSmithKlein, Eli Lilly and Company, AbbVie, Regeneron, and Medimmune receiving honoraria or fees; as a speaker for the Fall Clinical Dermatology Conference, Maui Derm, and Regeneron receiving honoraria or fees. Anne Marie Singh, MD, as an advisory board member for Incyte receiving honoraria. Peggy Wu, MD, MPH is an author for UpToDate, Inc receiving honoraria.