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CLINICAL AND IMMUNOLOGICAL PREDICTORS OF UNCONTROLLED ALLERGIC DISEASES IN CHILDREN AND ADULTS: THE ROLE OF BIOMARKERS, MICROBIOME, AND PERSONALIZED THERAPY

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ABSTRACT
Allergic diseases (asthma, allergic rhinitis, atopic dermatitis, and food allergy) share epithelial barrier dysfunction, type 2 immune activation, microbial dysbiosis, and age-dependent trajectories. A major challenge is early identification of patients who remain uncontrolled despite guideline-based therapy, as uncontrolled disease increases exacerbations, sleep disturbance, school and work impairment, systemic corticosteroid exposure, and anxiety. This narrative review synthesizes clinical and immunological predictors of uncontrolled allergic disease in children and adults, emphasizing biomarkers, microbiome-related mechanisms, and personalized therapy. Current concepts from international guidelines and literature (2020–2026) were analyzed. Poor control is predicted by high baseline disease activity, early-onset multi-organ atopy, recurrent exacerbations, polysensitization, type 2-high inflammation, barrier impairment, comorbidities (rhinosinusitis, obesity), persistent environmental exposure, psychological stress, and non-adherence. Biomarkers improve risk stratification only when interpreted with clinical context: blood eosinophils and fractional exhaled nitric oxide are useful in asthma; allergen-specific IgE and molecular components refine diagnosis in rhinitis and food allergy; and skin, blood, and microbiome markers may phenotype atopic dermatitis. Microbiome dysbiosis helps explain how early-life exposures, antibiotics, diet, epithelial injury, and *Staphylococcus aureus* colonization shape allergic severity, although it is not a standalone diagnostic test. Personalized therapy integrates treatable-trait assessment, allergen immunotherapy, biologics targeting IgE, IL-5/IL-5R, IL-4Rα, IL-13, and TSLP, and anti-IgE-based risk reduction in selected food allergy patients. Future care requires a life-course model integrating phenotype, endotype, biomarkers, exposure history, and patient behavior.

KEYWORDS: allergic disease; biomarkers; microbiome; biologics; personalized medicine; uncontrolled disease.

INTRODUCTION

Allergic diseases are among the most common chronic inflammatory conditions in childhood and adulthood. In daily clinical practice they rarely appear as clean textbook entities. A child with atopic dermatitis may later develop food allergy, wheezing and allergic rhinitis; an adult with severe asthma may also have chronic rhinosinusitis, aspirin-exacerbated respiratory disease, obesity and anxiety; and a patient with food allergy may be clinically well until an unexpected exposure causes a severe systemic reaction. For this reason, the term uncontrolled allergic disease should be understood not simply as a failure of one medication, but as a multidimensional state in which symptoms, exacerbation risk, tissue inflammation, comorbidities, exposures and patient behavior remain insufficiently controlled [1-4].

The last decade has changed the language of allergy and clinical immunology. The older approach, centered on symptoms and broad anti-inflammatory treatment, has been complemented by phenotype- and endotype-driven thinking. Type 2 inflammation, epithelial alarmins, barrier defects, neuroimmune itch pathways, allergen molecular components and microbial ecology are now part of practical decision-making. This transition is especially visible in severe asthma and atopic dermatitis, where biologics have created treatment options for patients who previously depended on repeated systemic corticosteroids or non-specific immunosuppression [5-7].

At the same time, clinicians must remain careful. Biomarkers are helpful, but they are not clinical shortcuts. A high blood eosinophil count does not automatically mean severe asthma; an elevated total IgE does not prove that

a food is clinically dangerous; and microbiome changes may be a cause, consequence or marker of inflammation. The most reliable clinical judgement comes from combining disease history, objective measures, immunological data and the patient's lived context [8-11]. The goal of this article is to provide a practical, clinically oriented review of predictors of uncontrolled allergic disease in children and adults, with attention to asthma, allergic rhinitis, atopic dermatitis and food allergy.

1. Defining uncontrolled allergic disease

Uncontrolled allergic disease can be defined as persistent symptoms, frequent reliever use, repeated exacerbations, impaired sleep or activity, ongoing tissue inflammation, treatment-related toxicity, or high risk of severe reaction despite appropriate diagnosis and therapy. This definition is intentionally broader than the word severe. A patient may have mild disease that is uncontrolled because of continued allergen exposure or poor adherence; conversely, a patient with biologically severe disease may become well controlled when the correct target is treated [12, 13].

In asthma, poor control includes daytime symptoms, night waking, activity limitation, excessive reliever use, low lung function and future risk of exacerbations. Severe asthma is a smaller subset in which disease remains uncontrolled despite optimized high-dose controller therapy, or worsens when such therapy is reduced [14, 15].

In allergic rhinitis, uncontrolled disease is reflected by nasal obstruction, rhinorrhea, sneezing, itching, sleep disturbance, ocular symptoms and impaired school or work performance despite intranasal corticosteroids, antihistamines or allergen avoidance [16]. In atopic dermatitis, poor control is expressed through itch, sleep loss, flares, infected lesions, psychosocial burden and inadequate response to topical anti-inflammatory therapy or systemic agents. In food allergy, control is less about daily symptoms and more about preventing accidental exposures, reducing reaction severity, maintaining nutrition and improving quality of life [17, 18].

Across diseases, the first step in evaluating poor control is not escalation but verification. Clinicians should confirm the diagnosis, assess adherence and technique, review exposure, screen comorbidities and estimate inflammatory phenotype. This is particularly important in children, where viral wheeze, dysfunctional breathing, reflux, chronic infection, immunodeficiency and anxiety may mimic or complicate allergic disease. In adults, occupational exposure, smoking, chronic rhinosinusitis, obesity, non-steroidal anti-inflammatory drug sensitivity and medication side effects often explain apparent treatment resistance [19].

2. Shared immunological architecture: from barrier injury to type 2 inflammation

The allergic response begins at barrier surfaces: airway epithelium, nasal mucosa, skin and gastrointestinal mucosa. These tissues are not passive walls. They sense allergens, pollutants, viruses, irritants and microbial products, then release epithelial cytokines such as thymic stromal lymphopoietin, IL-25 and IL-33. These alarmins activate dendritic cells, type 2 innate lymphoid cells and T helper 2 cells, promoting IL-4, IL-5 and IL-13 responses. The result is class switching toward IgE, eosinophil maturation and recruitment, mucus production, tissue edema, itch, bronchial hyperresponsiveness and barrier dysfunction [20-22].

This pathway explains why different allergic diseases cluster in the same patient. IL-4 and IL-13 drive IgE production and barrier abnormalities; IL-5 maintains eosinophilic inflammation; TSLP may sit upstream of several type 2 circuits; and IL-31 contributes to itch in atopic dermatitis. However, allergic inflammation is heterogeneous. Some patients show neutrophilic, mixed or paucigranulocytic asthma; some adults with atopic dermatitis have less classical type 2 signatures and more chronic lichenified disease; and food allergy may involve IgE-mediated, non-IgE-mediated or mixed mechanisms [23-25].

Age modifies this biology. Infancy is characterized by immune maturation, microbiome development and barrier vulnerability. Childhood allergic disease often follows an atopic march pattern, although not every child follows a linear trajectory. Adolescence introduces adherence problems, hormonal change and psychosocial stress. Adult-onset disease may be less dominated by classical allergen sensitization and more influenced by occupational irritants, chronic rhinosinusitis, obesity and epithelial alarmin pathways. Therefore, predictors of poor control must be interpreted across the life course rather than copied from one age group to another [27-29].

3. Clinical predictors across the allergic disease spectrum

Several clinical predictors repeatedly signal a higher probability of uncontrolled disease. First, early onset and multi-morbidity matter. Children with moderate-to-severe atopic dermatitis, early food sensitization, recurrent wheeze and allergic rhinitis require close follow-up because multi-organ atopy often reflects a stronger systemic type 2 tendency [30]. Second, a history of severe exacerbations is one of the most reliable predictors of future exacerbations, particularly in asthma and food allergy [31]. Third, persistent exposure to allergens, tobacco smoke, indoor dampness, air pollution, occupational sensitizers or irritants can maintain inflammation even when pharmacological treatment is technically appropriate [32].

Fourth, comorbidities often drive poor control. Allergic rhinitis worsens asthma symptoms and sleep; chronic rhinosinusitis with nasal polyps can identify a type 2-high airway phenotype; obesity and gastroesophageal reflux may amplify dyspnea; and anxiety can increase symptom perception and avoidance behavior. In atopic dermatitis, skin infection, sleep deprivation and psychological distress create a self-reinforcing cycle of itch and inflammation. In food allergy, poorly controlled asthma remains an important safety concern because respiratory compromise can complicate anaphylaxis [33-35].

Fifth, adherence is a central predictor. Many patients labelled as difficult-to-treat have suboptimal inhaler technique, irregular intranasal corticosteroid use, steroid phobia, fear of systemic therapy, poor access to medications or unrealistic expectations. In children, the caregiver's understanding of the disease is as important as the child's biology [36,37]. In adolescents, embarrassment, denial and inconsistent routines often become the hidden drivers of uncontrolled disease [38,39].

Table 1. Cross-disease predictors of poor control in allergic disease

Predictor domain	Clinical signal	Immunological / biological interpretation	Practical implication
Disease burden	Frequent flares, night symptoms, reliever overuse, school/work impairment	Persistent inflammation and high future risk	Reassess diagnosis, adherence, exposure and phenotype before escalation
Atopic profile	Early onset, polysensitization, multi-organ atopy	Systemic type 2 predisposition and barrier dysfunction	Monitor for progression and consider integrated allergy care
Biomarkers	High eosinophils, high FeNO, relevant specific IgE, component positivity	Type 2 inflammation or clinically meaningful sensitization	Select targeted therapy or immunotherapy only in context
Comorbidities	Rhinitis, sinusitis, obesity, infection, sleep disturbance, anxiety	Non-allergen drivers may amplify symptoms	Treat comorbidities as modifiable traits
Microbiome/barrier	S. aureus colonization, recurrent infection, early antibiotic exposure, dysbiosis	Barrier inflammation and altered immune education	Avoid unnecessary antibiotics; optimize barrier repair and infection control
Behavior and access	Poor adherence, incorrect device use, fear of therapy, limited follow-up	Apparent resistance without true biological refractoriness	Shared decision-making, education and simpler regimens

4. Biomarkers: clinical value and limitations

IgE and allergen-specific sensitization

IgE remains the classical biomarker of allergic disease, but its interpretation is often misunderstood. Total IgE reflects atopic tendency, parasitic exposure, some immunodeficiencies and disease activity in certain patients; it is not a diagnostic test for a specific allergy [40]. Allergen-specific IgE and skin-prick testing detect sensitization, which must be matched to clinical symptoms. A positive result without compatible exposure-related symptoms is not equivalent to disease [41, 42].

In allergic rhinitis and food allergy, the strength of specific IgE and the pattern of molecular sensitization can refine risk assessment. Component-resolved diagnostics may distinguish primary sensitization from cross-reactivity, for example storage proteins associated with more persistent or systemic reactions versus pollen-related labile proteins that more often cause oral allergy symptoms. In asthma, IgE-mediated sensitization is relevant when considering allergen exposure, environmental control, allergen immunotherapy and anti-IgE therapy. Nevertheless, IgE is not a universal severity marker. Some patients with severe asthma have low IgE; some patients with high IgE have mild disease [43-45].

Eosinophils

Blood eosinophils are among the most practical biomarkers in allergic medicine because the test is inexpensive, repeatable and biologically meaningful. In asthma, elevated blood eosinophils are associated with exacerbation risk and with response to anti-IL-5, anti-IL-5 receptor and, in many patients, anti-IL-4R alpha therapy [46-48]. Sputum eosinophils remain closer to airway pathology but are less available in routine practice. Tissue eosinophils are important in eosinophilic esophagitis and some chronic rhinosinusitis phenotypes [49].

Eosinophils should be interpreted carefully. Counts fluctuate with systemic corticosteroids, infections, circadian rhythm, season and biologic treatment. A single normal value does not exclude type 2 disease, especially in a patient recently treated with oral corticosteroids [50-52]. Conversely, eosinophilia may indicate parasitic infection, drug reaction, eosinophilic granulomatosis with polyangiitis or hematologic disease. In the clinic, the most useful question is not 'is the eosinophil count high?' but 'does the eosinophil pattern explain the patient's current risk and guide a modifiable treatment decision?'

Fractional exhaled nitric oxide

Fractional exhaled nitric oxide is a non-invasive marker of IL-13-driven airway epithelial activation. In asthma it can support the diagnosis of type 2 airway inflammation, identify corticosteroid responsiveness, detect poor adherence to inhaled corticosteroids and contribute to biologic selection [53-55]. High FeNO in a patient using inhaled corticosteroids may indicate persistent type 2 inflammation, continued allergen exposure, inadequate dosing, incorrect technique or non-adherence. In children, FeNO can be particularly useful because spirometry may be variable and symptom reporting is caregiver-dependent [56].

FeNO is not specific for asthma. It may be elevated in allergic rhinitis and atopy and reduced by smoking. It should not replace spirometry, bronchodilator reversibility or clinical assessment. Its strongest role is in a multidimensional algorithm: symptoms, exacerbations, lung function, eosinophils, allergen sensitization and treatment history [57].

Periostin, cytokines and emerging biomarkers

Periostin, a matricellular protein induced by IL-13, was an early candidate biomarker of type 2 asthma and airway remodeling. Although it has biological appeal, routine clinical use remains limited by assay availability, age effects and imperfect specificity. Cytokine profiling, transcriptomics, proteomics and metabolomics are scientifically promising but are not yet ready for broad routine use in most allergy clinics [58].

In atopic dermatitis, candidate biomarkers include serum thymus and activation-regulated chemokine, eosinophil-derived proteins, IL-13-related signatures, skin barrier proteins, natural moisturizing factor and microbial signatures. In food allergy, basophil activation testing and component testing may improve diagnostic precision and reduce unnecessary oral food challenges, but availability varies [59]. The practical future is likely not a single biomarker, but a composite score integrating clinical severity, molecular sensitization, inflammatory markers and digital longitudinal outcomes [60].

5. Disease-specific predictors

Bronchial asthma

Uncontrolled asthma is predicted by prior severe exacerbations, poor symptom control, reduced lung function, high reliever use, oral corticosteroid exposure, comorbid rhinitis or sinusitis, smoking, obesity, occupational exposure and persistent type 2 inflammation [61]. In children, repeated emergency visits, viral-triggered severe wheeze, aeroallergen sensitization, eczema and food allergy increase concern for future risk. In adults, late-onset eosinophilic asthma and chronic rhinosinusitis with nasal polyps often signal a phenotype that may respond to biologic therapy [62-64].

The practical assessment should follow a treatable-traits framework. Confirm variable airflow limitation; check inhaler technique and adherence; identify allergens and irritants; assess rhinitis, sinusitis, reflux, obesity and sleep; and measure blood eosinophils, FeNO and IgE where relevant. Patients with uncontrolled type 2-high asthma despite optimized high-dose inhaled corticosteroid therapy may be candidates for biologics. Anti-IgE therapy is most relevant in allergic asthma; anti-IL-5 and anti-IL-5R therapy in eosinophilic asthma; anti-IL-4R alpha therapy in type 2 asthma with eosinophilic or FeNO-high features; and anti-TSLP therapy may be useful across broader inflammatory profiles [65-67].

A key clinical mistake is to treat biomarkers instead of patients. A biologic should be chosen according to exacerbation history, biomarker profile, comorbid disease, age, safety, dosing preference and access. The endpoint should be meaningful control: fewer exacerbations, less systemic corticosteroid exposure, improved lung function and better daily life, not simply a lower eosinophil count [68].

Allergic rhinitis

Allergic rhinitis is often underestimated because it is not usually life-threatening, yet uncontrolled rhinitis can dominate quality of life. Nasal obstruction, sleep fragmentation, fatigue, reduced concentration and coexisting conjunctivitis may impair children's school performance and adults' work productivity. Rhinitis also worsens asthma control; therefore, persistent upper airway inflammation should be treated as part of a united airway model rather than as a minor comorbidity [69]. Predictors of uncontrolled rhinitis include polysensitization, persistent perennial allergen exposure, severe nasal obstruction, chronic rhinosinusitis, adenoid hypertrophy in children, incorrect intranasal spray technique, underuse of intranasal corticosteroids and unrealistic reliance on oral antihistamines alone [70]. Biomarkers are less central than in severe asthma, but specific IgE and component testing can identify relevant allergens for avoidance and immunotherapy. Allergen immunotherapy remains the only disease-modifying option for selected patients with clinically relevant IgE-mediated sensitization, especially when symptoms are persistent despite pharmacotherapy or when the patient seeks long-term modification rather than temporary relief [71-73].

Atopic dermatitis

Atopic dermatitis is a visible, itchy, barrier-driven inflammatory disease with systemic consequences. Predictors of uncontrolled disease include early onset, severe baseline eczema, filaggrin-related barrier impairment, recurrent skin infection, S. aureus colonization, high itch intensity, sleep disturbance, food sensitization in young children,

psychosocial stress and steroid phobia. In adults, chronic hand eczema, occupational irritants and long-standing lichenification often complicate control [74-77].
The immune profile of atopic dermatitis is dominated by type 2 inflammation, but it is not identical in all patients. IL-4 and IL-13 are central to barrier dysfunction, inflammation and itch amplification; IL-31 has a strong itch-related role; and chronic lesions may show broader immune activation. Biologics and small molecules have expanded treatment for moderate-to-severe disease [78-80]. Dupilumab, targeting IL-4R alpha signaling, has the longest experience and broad pediatric and adult use. IL-13-targeted agents such as tralokinumab and lebrikizumab, and IL-31 pathway blockade with nemolizumab in selected indications, illustrate a more granular approach to disease control [81-83].
Biomarkers for routine selection of atopic dermatitis therapy remain less mature than in asthma. Disease severity scores, itch, sleep, infection history, distribution, age and comorbid asthma or rhinitis remain central. Microbiome assessment is scientifically important, but routine sequencing is not yet required. Clinically, barrier repair, anti-inflammatory therapy, infection control, patient education and realistic long-term plans remain the foundation [84].

Food allergy
Food allergy differs from asthma, rhinitis and dermatitis because patients may be asymptomatic between exposures yet remain at risk for systemic reactions. Predictors of poor control include previous anaphylaxis, coexisting uncontrolled asthma, high-risk foods, multiple food allergies, high specific IgE or concerning component profiles, adolescence, poor label literacy, eating outside the home and lack of epinephrine preparedness. In infants and children, excessive dietary restriction can also become a form of poor control by impairing nutrition and family quality of life [85].
Diagnosis must avoid the trap of testing without history. Skin-prick testing and specific IgE are useful when the suspected food and clinical reaction are clear; broad panels can create false labels and unnecessary avoidance. Oral food challenge remains the diagnostic standard when history and testing are discordant or when tolerance is being assessed, but it requires appropriate setting and risk management. The 2024 PRACTALL update reflects the continued need to standardize oral food challenge procedures and improve safety [86-88].
Personalized food allergy care now includes component-resolved diagnostics, risk education, emergency plans, nutrition support and, in selected patients, immunomodulatory therapy. The approval and trial evidence for omalizumab in IgE-mediated food allergy marked an important shift: treatment can reduce the risk of reaction from accidental exposure, although it does not remove the need for avoidance or epinephrine readiness [89-91]. Oral immunotherapy may increase threshold doses for certain foods, but it also requires careful selection because gastrointestinal symptoms, anxiety, adherence and reaction risk may limit suitability [92].

Microbiome and allergic disease control
The microbiome offers a biological bridge between environment, barrier function and immune tolerance. Early-life gut microbiota maturation influences immune education, regulatory T-cell development, short-chain fatty acid production and mucosal barrier integrity [93]. Antibiotic exposure, cesarean delivery, low microbial diversity, diet, urban living and reduced farm-related microbial exposures have all been investigated as contributors to allergic risk. However, the relationship is complex. Microbiome changes can be causal, protective, compensatory or simply a marker of inflammation [94].
In asthma, airway and gut microbial patterns may influence viral susceptibility, neutrophilic inflammation and exacerbation risk. In allergic rhinitis, nasal microbial communities interact with epithelial inflammation and local immunity. In atopic dermatitis, the link is clinically obvious: flares often coincide with reduced microbial diversity and dominance of S. aureus, while effective anti-inflammatory treatment can restore a healthier skin microbial balance [95]. In food allergy, gut microbiome composition may influence oral tolerance, barrier function and response to immunotherapy [96].
Despite strong scientific interest, microbiome analysis is not yet a routine predictor of uncontrolled allergic disease. Current sequencing data are affected by sampling site, age, treatment, diet, geography and laboratory methods. Probiotics, prebiotics and microbial therapeutics remain attractive, but evidence is heterogeneous and disease-specific [97]. The practical message for clinicians is more conservative: protect the barrier, avoid unnecessary antibiotics, support balanced nutrition, treat infection appropriately and recognize that microbial ecology is part of a broader exposome rather than a standalone prescription [98-100].

7. Personalized therapy: from organ control to treatable traits
Personalized therapy begins with asking why this patient is uncontrolled now. The answer may be inflammatory, behavioral, environmental, anatomical, microbial or social. A child with uncontrolled asthma may need better inhaler technique and rhinitis treatment, not a biologic. An adult with high eosinophils, nasal polyps and repeated steroid bursts may need biologic therapy. A teenager with peanut allergy may need risk counseling, epinephrine confidence and psychological support as much as laboratory monitoring. A patient with severe atopic dermatitis may need a systemic anti-inflammatory plan and sleep restoration before any biomarker becomes meaningful.

The treatable-traits approach is useful because it converts complexity into action. Traits may include type 2 airway inflammation, eosinophilia, IgE-mediated sensitization, allergen exposure, epithelial barrier dysfunction, chronic infection, obesity, dysfunctional breathing, anxiety, poor adherence, incorrect device use and socioeconomic barriers. Each trait should have a measurable intervention and follow-up endpoint.

Biologics have made personalized therapy tangible. Omalizumab targets IgE and is relevant across allergic asthma, chronic spontaneous urticaria and, more recently, IgE-mediated food allergy. Mepolizumab, reslizumab and benralizumab target the IL-5/eosinophil axis. Dupilumab blocks IL-4 and IL-13 signaling through IL-4R alpha and can be valuable when asthma overlaps with atopic dermatitis or chronic rhinosinusitis. Tezepelumab targets TSLP, an upstream epithelial alarmin, and broadens the concept of intervention beyond downstream eosinophils [101-103]. In atopic dermatitis, IL-13 and IL-31 pathway therapies provide additional targeted choices. The challenge is no longer whether targeted therapy exists, but how to select the right patient, endpoint and timing.

Table 2. Biomarker-informed therapeutic orientation

Dominant signal	Typical clinical context	Potential targeted option	Caution
Allergen-specific IgE with compatible history	Allergic asthma, rhinitis, food allergy	Avoidance, immunotherapy where indicated, anti-IgE in selected cases	Sensitization alone is not disease
Blood eosinophilia / eosinophilic exacerbations	Severe asthma, nasal polyps, eosinophilic disease	Anti-IL-5 or anti-IL-5R; consider IL-4R alpha blockade	Exclude parasites, vasculitis and drug reactions
High FeNO despite controller therapy	Type 2 airway inflammation or poor ICS adherence	Optimize ICS use; consider type 2 biologic if severe	Affected by rhinitis, smoking and adherence
Barrier dysfunction with severe itch	Atopic dermatitis, recurrent flares	Barrier repair; IL-4/IL-13 or IL-31 pathway therapy where appropriate	Severity scores and patient burden remain essential
Microbial dysbiosis / S. aureus dominance	AD flares, infected lesions	Anti-inflammatory control, antiseptic measures, infection treatment	Routine sequencing is not yet standard
Multiple food allergy with accidental exposure risk	Children/adults with IgE-mediated food allergy	Education, epinephrine, dietary plan, anti-IgE or immunotherapy in selected patients	Therapy reduces risk but does not equal cure

8. Pediatric and adult differences

Children are not small adults in allergy medicine. Their immune systems, microbiome, airway size, skin barrier, diet and dependence on caregivers make prediction different. In children, uncontrolled disease often reflects caregiver understanding, school policies, fear of medication, viral exposures and growth-related concerns. Biomarkers also need age-aware interpretation: total IgE and eosinophil counts vary with age, and FeNO may be influenced by atopy and cooperation with testing [104].

Adults bring different problems: occupational exposures, smoking history, obesity, chronic rhinosinusitis, cardiovascular disease, polypharmacy, pregnancy considerations and long-term corticosteroid toxicity. Adult-onset eosinophilic asthma may be severe even without childhood allergy. Adult atopic dermatitis may be misdiagnosed as contact dermatitis, psoriasis or cutaneous T-cell lymphoma if the clinical pattern is atypical. Food allergy in adults often includes pollen-food allergy syndrome, shellfish allergy or persistent childhood allergy with established avoidance behaviors [105].

A life-course model is therefore essential. The clinician should identify whether the patient is in an immune-development stage, an atopic march stage, an adherence-risk stage, an occupational exposure stage or a comorbidity-dominant stage. Personalized therapy is not only molecular; it is developmental.

9. Proposed clinical algorithm

Step 1: Confirm the diagnosis using objective criteria where available: spirometry and variability for asthma; history plus sensitization for allergic rhinitis; clinical morphology and distribution for atopic dermatitis; history, IgE testing and oral food challenge when needed for food allergy.

Step 2: Define control and risk separately. A patient may have few daily symptoms but high future risk, as in food allergy or asthma with previous severe exacerbations.

Step 3: Identify modifiable drivers: adherence, device technique, allergen exposure, smoke, occupational irritants, infection, rhinitis, sinusitis, obesity, sleep disturbance and psychological stress.

Step 4: Perform biomarker assessment targeted to the clinical question: eosinophils and FeNO for asthma; specific IgE and components for rhinitis or food allergy; infection and severity markers for atopic dermatitis; selected advanced tests only when they will change management.
Step 5: Match therapy to treatable traits: anti-inflammatory optimization, allergen immunotherapy, biologics, barrier repair, infection management, dietary planning, immunotherapy or anti-IgE in selected food allergy patients.
Step 6: Reassess with patient-centered endpoints: exacerbations, sleep, itch, activity, lung function, corticosteroid exposure, nutritional adequacy, emergency readiness and quality of life.

10. Limitations and future perspectives

The evidence base for predicting uncontrolled allergic disease is uneven. Asthma has the most developed biomarker-treatment pathway, whereas atopic dermatitis and food allergy still rely more heavily on clinical phenotyping. Microbiome studies are promising but difficult to translate because methods, populations and definitions vary. Many biologic trials enroll selected patients who may not represent multimorbid real-world populations. Pediatric evidence is often extrapolated from adults, and access to biomarkers or biologics differs widely by region.
Future research should focus on composite prediction models that combine clinical data, biomarkers, digital symptom tracking, environmental exposure, microbiome profiles and patient-reported outcomes. Artificial intelligence may help identify hidden patterns, but only if datasets are diverse, longitudinal and clinically validated. The strongest models will likely predict not only who is uncontrolled, but why: persistent type 2 inflammation, poor adherence, microbial-barrier imbalance, high-risk exposure, comorbidity or social vulnerability.
Precision allergy medicine should also avoid widening inequity. A sophisticated biomarker is useful only when it leads to accessible care. Education, correct diagnosis, affordable inhaled and topical therapy, epinephrine access and environmental control remain as important as monoclonal antibodies.

CONCLUSION

Uncontrolled allergic disease is a dynamic clinical state produced by the interaction of immune endotype, epithelial barrier dysfunction, microbiome ecology, exposure, comorbidity and patient behavior. IgE, eosinophils, FeNO, molecular allergen components, cytokine signatures and microbiome patterns can all improve understanding, but none should be interpreted in isolation. The strongest predictor is usually a pattern: early and multi-organ atopy, repeated exacerbations, persistent type 2 inflammation, impaired barrier function, relevant exposure and inadequate response despite optimized basic care.
For the practicing allergologist-immunologist, the central task is to convert this pattern into action. Confirm the diagnosis, identify treatable traits, choose biomarkers that answer specific questions and match therapy to the patient rather than to the disease label alone. This approach moves allergy care toward a more humane and precise model: not simply suppressing symptoms, but restoring control, safety, sleep, participation and quality of life across childhood and adulthood.

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