REVIEW ARTICLE

Qualitative vs. quantitative atopic dermatitis criteria – in historical and present perspectives

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Abstract

This review summarizes historical aspects, clinical expression and pathophysiology leading to coining of the terms *atopy* and *atopic dermatitis*, current diagnostic criteria and further explore the possibility of developing quantitative diagnostic criteria of atopic dermatitis (AD) based on the importance of atopic features – subjective, objective, and those derived from laboratory tests – the new partly promising AD biomarkers. 'Atopy', introduced in 1923, denoted 'the sense of a strange disease without a precise place in the body'. A decade later, Sulzberger and Hill, first defined 'atopic dermatitis'. The pioneering well-recognized criteria, 'Hanifin & Rajka' (*Acta Derm Venereol*, **92**, 1980, 44), were developed empirically on 'clinical experience' and expert consensus. As opposed to the widely used, rather anamnestic 'UK Criteria' (1994), they have few formal validation studies, but appear to well embrace various atopic phenotypes. Pruritus, xerosis, typical morphology/distribution of dermatitis and tendency to a relapsing/chronic course are common basic features in AD criteria, whereas skin sensitivity, heredity and various ill-defined atopic stigmata also seem to comprise the atopic phenomenon. Specific pheno- and endotypes are now emerging potentially enabling us to better classify patients with AD, but the influence of these on the diagnosis of AD is so far unclear. Few diagnostic models use quantitative scoring systems to establish AD cases from normal population, which, however, may be useful to better study and manage this disease. Long-term prospective observational studies, from which few are available at this point, along with interventional studies, are a perquisite and will provide the best option to improve our understanding of its complex characteristics and etiology.

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Conflicts of interest

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Introduction

Atopic dermatitis (AD) is a common chronic and relapsing inflammatory skin condition. In the second half of the 20th century, a dramatic increase in AD was observed in parts of Western and Northern Europe, Africa and Eastern Asia.[1] AD typically clusters in families and many develop concomitant transient or persistent wheezing, asthma, rhino-conjunctivitis and food allergies, commonly referred to as the atopic diatheses. Altered immune function and barrier abnormality are key drivers of these diseases, with environmental factors likely being responsible for the increased prevalence. Genetic studies have demonstrated a strong association between filaggrin loss-of-function mutations, AD and presence of other atopic diatheses, and AD as an entity appears to be characterized by filaggrin deficient skin.[2–4]

Simpson *et al.*[5] recently evaluated the definition of AD among incident cases from 102 studies on primary prevention in AD, and showed that 27% did not provide criteria for defining incident cases. The widely utilized Hanifin & Rajka criteria[6] were applied in 27%, while a disease definition unique to the particular study was used in as many as 21%. While these data clearly demonstrate the discrepancy of the diagnostic criteria used to study AD, history and clinical experience have emphasized that the complexity of AD is much more than just 'atopy – yes or no?'.

This review article presents and summarizes the history of signs and symptoms leading to the coining of atopy and AD, and furthermore the development of various AD criteria over time. It also explores current knowledge and possibilities of future creation of quantitative diagnostic criteria of AD discriminating AD individuals from normal population, likely advancing us towards a better understanding and definition of this many-faced disease.

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First steps of defining atopy

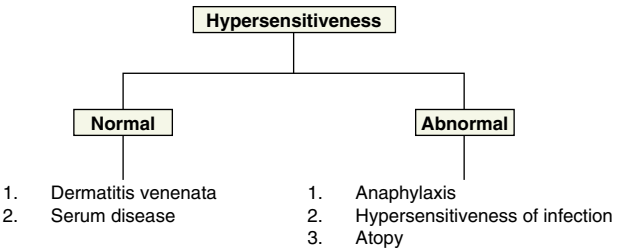
The term 'atopy' was coined in 1923 by pioneers of immunology Coca and Cooke,[7] as a part of a new definition of hypersensitiveness, defined firstly by Doerr in 1914.[8] In the paper: 'On the classification of the phenomena of hypersensitiveness' Coca and Cooke described hypersensitiveness solely as immunological reactions: 'a susceptibility in man or animal, that is mediated by a special mechanism', divided into normal and abnormal patterns (Table 1). Atopy was in category of abnormal immunologic patterns in man. The actual term 'atopy', from the Greek word 'a-topos', was coined in collaboration with E. Perry, professor in Greek language, to denote the sense of a strange disease without a precise place in the body. This first definition of atopic hypersensitiveness was divided into five criteria (Table 1) describing a phenomenon of heritable hypersensitivity to common environmental allergens often seen in patients with asthma and hay fever.

In 1925, Coca and Grove proposed calling the substances responsible for the passive transfer of allergies for 'atopic reagins'.[9]

Regarding the very first traces of exploring heredity of allergic diseases, Hippocrates observed relationship between allergies and genetic factors, but it was in the classical report 'Human sensitization' from 1916 that Cooke and Vander[10] performed the first systematic study on genetics and clinical manifestations of sensitization such as asthma/allergic rhinitis and concluded that the tendency to become allergic seemed to be hereditary. The issue of defining the dermatitis disease that they observed, later known as AD, already caused problems at this stage; they did not include dermatitis because they found it too difficult to consistently diagnose this condition.

Table 1 Classification of hypersensitiveness and the first classification of atopic hypersensitiveness – according to Coca and Cooke[7]

The Coca and Cooke classification of hypersensitiveness



The first classification of atopic hypersensitiveness

1. Is exhibited against non-precipitinogenic substances as well as against precipitinogenic substances
2. Has not been shown to be passively transferable to normal individuals with the blood of sensitive individuals
3. Can be greatly lessened but not completely removed by the suitable injection of the active substance
4. Is inherited, subject to a dominant gene
5. Is expressed in pathological changes the more important of which are different from those of the anaphylactic reaction in the guinea-pig, the rabbit or the dog

Introducing atopic dermatitis

Hippocrates probably described chronic pruritic conditions consistent with AD, but first traces of the atopic skin disease probably came from the Roman historian Suetonus' (born about year 69 after Christ) description of Emperor Augustus.[11] He suffered from pruritic dry skin patches and from seasonal respiratory disorders and the tendency ran in the family. Table 2 provides landmarks in AD history.

'Porrigo larvalis', a disease described by Willan and Bateman in 1816, has been identified as one of the earliest descriptions of AD.[12,13] Later, E. Wilson described at the 1856 Meeting of the British Medical Association 'infantile eczema' as a disease with onset at 4–6 weeks, several lesion morphologies, and transferred by breast milk.[14]

Along with Broncq, Jacquet and Rost, Besnier was a pioneer in the more modern AD description.[15] He reported about 'prurigo diathésique' with pruritus –itch, as the major symptom: 'le symptôme premier et le premier symptôme est le prurit' and the accompanying skin lesions not being specific, internal manifestations such as emphysema, bronchial asthma, rhinitis and gastrointestinal disturbances could occur, a hereditary predisposition and the disease was not restricted to lower social classes.

A decade after introduction of 'atopy', Sulzberger and Wise coined the term 'atopic dermatitis'[16] practically listed as a footnote in the '1933 Year Book of Dermatology and Syphilology' (Table 3). They defined a disease distinct from contact and seborrhoeic eczema, pruritic and lichenified conditions. Their AD clinical and paraclinical highlights comprised a condition preceded by infantile eczema, with dermatitis characterized by absence of vesicles, and with predilection for flexural areas; the antecubital, popliteal and neck folds. The face, in particular the eyelids were affected. There was often an atopic family history, they had usually negative patch tests to irritants and many positive immediate skin reactions (by scratch or intradermal tests) with many 'reagin's' – later known as antibodies, in the blood.

Two years later (1935), Sulzberger along with Hill postulated[17] that the fundamental basis of AD is the same at all ages: 'The infant is not merely a small man: He is a different sort of small man (. . .) it is not strange, then, that atopic dermatitis is not similar in clinical appearance at different age periods. It would be strange if it were similar'. They described clinical highlights, both clinical and the development of sensitivity by immediate type skin tests in different ages and delineated three stages.

They postulated atopic hypersensitivity to common food items and aerosols as the consistent link unifying AD, regardless of clinical appearance or age of the patient. They described loss and gain of sensitivity during the atopic life, often with predominance of the food allergens; eggs, milk and wheat in early life,

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developing towards dominance of common aerosols. They also observed that patient's sensitivities not always were relevant, as the skin condition did not improve with avoidance of assumed allergic components and, at the same time, observed patients eating what they wanted disregarding their 'food-allergies' without a dermatitis flare. Another important issue linking to the discussed allergens, was the paradox of the atopic baby with eczema apparently having food allergies demonstrated by positive immediate skin tests to e.g. egg, without ever being exposed to such food.

The first stage, 'infantile eczema of atopic type' (0–2 years), described the atopic symptoms commonly started with a tendency to cradle cap and rash on the cheeks. This progressed to itching rash of different morphes on the outer aspects of the lower part of the legs, forearms, wrists and forehead. In the second stage, 'atopic dermatitis of childhood' (2–12 years), they described remission for 'a great many' of the children before the third year of life, but also disease onset for others. Common sites of the polymorphous dry, scaly, infiltrated and lichenified eruptions were described as the antecubital and popliteal spaces, wrists and neck. Children suffered from continuous and intense itching leading to scratching and rubbing and secondary traumatic change. In the third stage: 'atopic dermatitis of the adult' the authors described AD cases either as a continuous disease spectrum or as a course with intermittent exacerbations and remissions.

'Modern' etiologies of atopy

In the first half of the 20th century, immediate type allergy was thought to be the primary etiology of AD. As discussed, diet management and desensitization of patients provided little help. Patients had, on the other hand, extensive use of topical corticosteroids, introduced in 1951.[18]

In the 1960s, new atopy theories were explored. The beta-blockade theory by Szentivanyi[19] indicated a gene defect in catecholamine/beta-adrenergic homeostasis in the skin of atopics. It was hypothesized that a reduction in the beta-adrenergic stimulation in AD patients causing abnormal vascular responses, decreased pruritic threshold and lichenification.[20,21] Later studies questioned this hypothesis, as data demonstrated that alterations in the beta-adrenergic system possibly was a consequence rather than a cause of atopic disease.[22]

With the 1966 Ishizakas's discovery[23] that the IgE molecule as the 'allergy reagin' and at the same time the discovery of high IgE levels in patients with AD,[24] exploration of IgE's role in activating mast, eosinophil and dendritic cells in atopic patients was further explored in the last part of the 20th century.

Focus on immunological and inflammatory processes as the etiology of AD has been re-challenged since 2006 following the identification of filaggrin gene null-mutations as strong predictors of AD and other atopic diatheses by Palmer *et al.*[2] Most now recognize both immunological and barrier problems as contributing factors in the etiology of AD and other atopic diseases.[25]

Creation of atopic dermatitis diagnostic criteria

Development of AD criteria

Table 4 provides an overview of various diagnostic criteria of AD introduced over time, the method used for their development and number of literature citations.

In two of the criteria, Rajka[26] and Lillehammer,[27] the method of development is not clearly explained, but refers to practical experience, previous clinical and laboratory studies without further explanation. Five criteria, Hanifin & Lobitz[28] Hanifin & Rajka,[6] Tagami,[29] The International Study of Asthma and

Table 2 Important pioneers, thinkers and observers of the 'beginning' of atopic dermatitis

Year	Pioneers	Highlights
	Hippocrates	Described itchy chronic conditions and observed relationship between allergies and heredity
A.D. 69	Suetonus	Described emperor Augustus' family history of itchy skin disease, seasonal respiratory disorders and hereditary
1816	Bateman and Willan	Described 'Porrigo larvalis'. Considered as one of the earliest descriptions of atopic dermatitis (AD)
1856	William	Introduced 'Infantile ezcema'. Onset at age 4–6 weeks, several lesion morphologies, and transferred by breast milk
1892	Besnier	'Prurigo diathésique'. Itchy skin disease with different morphology, sometimes accompanied by asthma and hay fever. Tendency to heredity
1923	Coca and Cooke	Coined the term 'atopy' as 'susceptibility in man' by a pattern of a heritable hypersensitiveness to common allergens seen in patients with hay fever and asthma
1933	Wise and Sulzberger	Coined AD (Table 3)
1935	Hill and Sulzberger	Stated the fundamental basis of AD is the same in all ages. No vesicles observed. Described gain and loss of sensitivity during life *Infantiles*: Tendency to cradle cap, rash on cheeks, outer aspects of legs, arms, wrists and head *Childhood*: Dry, scaly, infiltrated, lichenified eruptions at antecubital and popliteal spaces, wrists and neck region *Adults*: Also polymorphous eruptions at flexural regions and forehead especially the eye region
1968	Ishizaka and Ishizaka	Discovery of the IgE molecule to be the allergy reagin
1980	Hanifin and Rajka	Introduced the first widely utilized diagnostic AD criteria
2006	Palmer *et al.*	Discovery of filaggrin's role in AD barrier defect

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Table 3 The 1933 coining of atopic dermatitis by Wise and Sulzberger[16]

1.	Atopic family history
2.	Antecedent infantile eczema
3.	Localization in antecubital and popliteal spaces, anterior of the neck and chest and face, particularly the eyelids
4.	Presence of a grayish or brownish coloration of the skin
5.	Absence of true vesicles, clinically and histologically
6.	Vasomotor instability or irritability
7.	Usual negative patch test with many contact irritants
8.	Many positive reactions of immediate weal type to scratch or intradermal testing
9.	Presence of many reagins in the blood serum

Allergies in Childhood (ISAAC)[30] and Millennium criteria 1998[31] were made according to communication, expert consensus or literature review. Four criteria, Kang & Tian,[32] UK criteria,[33] The 1996 Diepgen criteria[34] and Danish Allergy Research Centre (DARC) criteria[35] were developed in the context of well-described clinical studies.

Hanifin & Rajka diagnostic features of atopic dermatitis

Hanifin and Rajka are considered pioneers of the first widely utilized diagnostic AD criteria created in 1980[6] (Table 5). These were evolved based on previous suggestions of criteria published individually by both authors,[26,28] 'suggestions by various individuals' and discussions among experts during the 1979 first AD International Symposium. The comprehensive criteria consist of four basic and 23 minor features. Patients need at least three basic and three minor features to fulfill these criteria. The authors considered the basic feature pruritus –itch, as central: 'The diagnosis of active atopic dermatitis cannot be made if there is no history of itching' and 'since a primary cutaneous lesion has never been firmly established, it may that all the cutaneous changes are secondary to itch-induced scratching'.

Hanifin and Rajka's work is considered of particular importance – it was the 11th most cited article in dermatologic literature 1945–90[36] and had by June 2014 more than 800 citations according to Web of Science.

As reviewed by Simpson,[5] the Hanifin & Rajka criteria are presently still widely used as definition of AD in clinical studies, but have only been validated in two studies[37,38] with a total of 363 patients finding sensitivities of 93–96% and specificities of 78–94%.

The 1994 UK criteria

The well conducted 1994 UK criteria, designed to be used in larger epidemiological studies[33,37,39] are, according to Brenninkmeijer *et al.*,[40] the most validated with 19 validation studies, however, with large variations in sensitivities (10–100%) and specificities (89–99%) depending on the number of included minor criteria. They were developed by a method where 16 physicians (dermatologists and other physicians with interest in AD) selected 10 cases of typical mild/moderate AD and 10 controls with another inflammatory skin diseases. The criteria were calculated by multiple logistic regression techniques from the most frequent anamnestic, subjective and objective features found in cases with the less inter-observatory difference. The original study was followed by a validation study before publication. The final criteria consist of a mandatory criterion; an itchy skin condition accompanied by a least 2–3 minor criteria (Table 4). Notable, there is only one criterion containing an objective sign – visible dermatitis. When compared to the Hanifin & Rajka basic criteria, they share: 'itchy condition', 'atopic personal/family history' and 'typical flexural (forehead in toddlers) distribution', whereas UK criteria also studied and found the minor Hanifin & Rajka criterion 'early onset' as a cardinal feature. Objective xerosis obtained one of the highest scores separating cases from controls, but was rejected because of unsatisfactory between-observatory repeatability; however, the anamnestic 'history of general dry skin' was included.

The ISAAC criteria

The 'shift' towards anamnestic or 'a question-only-format' criteria suitable for greater population-based epidemiological studies, aiming to be sufficiently sensitive to capture also the milder AD cases, were further accomplished with the ISAAC questionnaire.[30] They are solely anamnestic (Table 4) and described as developed in parallel to the UK criteria, operating with 'eczema' and AD/atopic eczema as synonyms, though, having 'atopic' distribution of the 'itchy rash' as a criterion.[41]

These criteria, utilized worldwide to determine the atopic prevalence, has shown great variations.[42] This can be due, obviously, to true disease variation prevalence, but this can also be caused by problems with questionnaire translation due to e.g. cultural differences. For this well-cited questionnaire (1517 Web of Science citations), there has only been one independent validation study[43] comprising all questions. In 1258 Ethiopian children, a positive predictive value of 49% and a negative predictive value of 91% were shown. Sensitivity and specificity estimates were not calculated.

A study[44] conducted by the ISAAC authors compared flexural eczema diagnosed by the ISAAC questionnaire vs. a standardized skin examination protocol in 30 358 children in 18 countries and found higher point prevalence by questionnaire (9%) than by physical examination (4%). A Polish study[45] supports the fact that the ISAAC criteria presumably embraces a range of other pruritic skin conditions. They examined 143 children and adolescents, with positive answers to the eczema questions by the ISAAC questionnaire, by physical examination and patch test with the European baseline series. They found a large coexistence between AD, defined by Hanifin & Rajka criteria, and allergic contact dermatitis (ACD), defined as contact allergy confirmed by a clinically relevant positive patch test result in combination

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with exposure history, dermatitis history and dermatitis pattern (if present at the time point of the examination), with tendency to decreased AD and increased ACD with age. Interestingly, 20% of children and 52% of adolescents with flexural eczema, according to the ISSAC questionnaire question 3, were ultimately diagnosed with ACD without evidence for AD.

Table 4 The 11 most historically interesting, utilized, cited and validated AD diagnostic criteria over time deemed by the authors

Authors – Criteria – Year	Development of AD criteria	Diagnostic criteria	No. of citations*
Rajka – Diagnosis of AD – 1975[26]	Combination of data and signs collected in the book 'Atopic dermatitis'	7 major and 7 minor criteria in total. 2 major and a further major or minor criterion present to diagnose	–
Hanifin and Lobitz – Newer concepts of AD – 1977[28]	Communication with investigators studying the disease	3 absolute criteria (pruritus, typical morphology and distribution, tendency to chronicity) plus ≥2 of 4 features or ≥4 of 9 features	232
Hanifin and Rajka – Diagnostic features of AD – 1980[6]	Practical experience, suggestions from various individuals, discussions during a symposium	3 major + 3 minor. 27 features in total (Table 5)	809
Kang and Tian – AD – An Evaluation Clinical and Laboratory Findings – 1987[32]	372 Chinese children with AD according to the Hanifin & Rajka criteria compared to 213 caucasian persons, some with skin disease, some from kindergarden, no further characteristics	2 basic features: –Pruritus, chronic or chronically relapsing dermatitis in characteristic areas. –Personal or family history of atopy 3 groups of minor features: –Genetic associations (early onset, xerosis/ichtyosis/palmar hyperlinearity) –Immunologic associations (type I reactions/tendency to infections) –Pharmaco-psysiologic associations (facial pallor/white dermographism/delayed blanch/periorbital darkening/perifol. Accentuation/tendency to nonspecific hand and foot dermatitis Either 2 basic features OR the first basic and 3 minor features	34
Schultz Larsen, Diepgen and Svensson – Lillehammer criteria – 1994[27]	Based on 'previous clinical and lab. studies centered on the diagnostic features of AD.' Does not identify which ones	Separates criteria in infantile (0–2 years), childhood (2–12 years) and adult phase based on the regions of visible eczema To fulfill criteria: Eczema in one age-dependent region and at least one positive of the anamnestic (history of relapsing course/seasonal variation, dry skin, itching when sweating wool intol resp. atopy/pos. family history of atopy in 1st degree family) or laboratory criteria (serum IgE or skin prick test). At least 3 features in total for diagnosis and duration of 6 weeks (infantile) or 3 months childhood/adult	–
Williams *et al.* – UK criteria for AD – 1994[33]	16 physicians selected 10 cases of typical mild/moderate AD and 10 controls with another inflam. skin disease (120 cases, and 102 controls). Criteria derived of the most frequent features with the less inter-observator difference. Followed by a validation study	Must have: –An itchy skin condition (or parental report of scratching or rubbing in a child) Plus 3 or more of the following: –History of involvement of the skin creases such as folds of elbows, behind the knees, fronts of ankles or around the neck (including cheeks in children under 10) –A personal history of asthma or hay fever (or history of atopic disease in a first-degree relative in children under 4) –A history of a general dry skin in the last year –Visible flexural eczema (or eczema involving the cheeks/forehead and outer limbs in children under 4) –Onset under the age of 2 (not used if child is under 4)	418
Tagami *et al.* – Japanese Dermatological Association criteria for the diagnosis of AD – 1995[29]	Task force with specialists in AD. 6 meetings in 6 months (consensus)	3 mandatory criteria for a definite AD diagnosis (pruritus, typical morphology and distribution, chronic course)	–

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Table 4 *Continued*

Authors – Criteria – Year	Development of AD criteria	Diagnostic criteria	No. of citations*
Asher *et al.* – ISAAC – 1995[30]	Questionnaire derived from the UK criteria that were developed in the same period	Question 1. 'Has your child ever had an itchy rash which was coming and going for at least 6 months?' Question 2. 'Has your child had this itchy rash at any time in the last 12 months?' Question 3. 'Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, around the neck, around the ears or eyes?' Positive response to the 3 questions is diagnostic of atopic eczema	1517
Diepgen, Sauerbrei and Fartasch – Development and validation of diagnostic scores for AD – 1996[34]	2 studies – original and validation (with other dermatological patients as controls). 3 sets of criteria AD cases defined by (three) relapses of flexural eczema	≥10 points: AD <3 points probably not AD 7–13 features in total depending on set of criteria	81
Bos, Van Leent and Sillevis Smitt – Millennium criteria for the diagnosis of AD – 1998[31]	Reviewed from literature	Allergic specific IgE mandatory plus 2 out of 3 clinical criteria (pruritus, typical morphology/ distribution and chronic/chronically relapsing). 21 additional non-mandatory features in 4 categories (eczema, dry skin, extra skin folds and ophthalmological pathology)	66
Jøhnke *et al.* – DARC – 2005[35]	Prospective study from birth to 18 months comparing 5 criteria	3 mandatory features. – Personal history of present/ past itching during the last 3 months or visible itching and scratching effects at the time of clinical examination. – Eczema in ≥2 of 4 skin regions at the time of clinical examination or a personal history of eczema localized in ≥2 of 5 skin regions during the last 3 months. – History of a continuing itchy eczema during the past 6 weeks	33

*According to Web of Science, September 2014.

The Millennium criteria

The 1998 Millennium criteria,[31] developed by review of the literature, are unique in their proposal of current or historic allergic-specific serum-IgE or skin prick test (SPT) to a 'reasonable panel' as mandatory criterion. They found IgE dysregulation as being central in AD pathogenesis, caused by gene defects. Patients fulfilling two of three clinical criteria, but not the mandatory criterion, would be referred as 'constitutional eczema', without referring to atopy.

A noteworthy exception: the 1996 Diepgen diagnostic scores for AD

Most criteria generally consist of several features/questions, of which the atopic patient must satisfy to have AD. They must all be considered as qualitative criteria as they aim to diagnose AD binary as 'yes or no?'.

A remarkable exception, the 1996 Diepgen criteria,[34] were derived from a validation study based on 21 AD features basically taken from the Hanifin & Rajka criteria. They divided the atopic features in 'subjective', 'objective' and 'laboratory tests'. Division into 'subjective' and 'objective' features was based on what two 'experienced physicians' would expect had low (subjective) or high inter-observatory (objective) agreement. Examples of subjective features included thinning of the lateral eyebrow – Hertoghe's sign, hyperlinear palms and food intolerance. Examples of objective features included what we would expect as anamnestic data like a family history of atopic disease and wool intolerance, but also a range of 'true' objective signs like dry skin. They intended to develop AD score systems with high discriminative ability between cases (defined by (preferably) three relapses of flexural eczema) and controls via logistic regression models and backward elimination of the weakest features by creating estimates; β, representing the influence of the various AD features. A β-value <1.5 corresponded to 1 atopic point, a β-value between 1.5–2.5 corresponded to 2 points, whereas a β-value >2.5 generated 3 points.

The 'original' case-control study was performed with 245 AD cases (median age: 22 years, range 10–54) and 618 controls (median age: 23 years, range 18–52) from the general population. They developed three scoring systems; a model without constrains ('subjective', 'objective' and laboratory tests), a model

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Table 5 The 1980 Hanifin & Rajka diagnostic criteria of atopic dermatitis[6]

Must have 3 or more basic features:	Pruritus
	Typical morphology and distribution: –Flexural lichenlification or linearity in adults –Facial and extensor involvement in infants and children
	Chronic or chronically relapsing dermatitis
	Personal or family history of atopy (asthma, allergic rhinitis, AD)
Plus 3 or more of minor features:	Xerosis
	Ichthyosis/palmar hyperlinearity/keratosis pilaris
	Immediate (type I) skin test reactivity
	Elevated serum IgE
	Early age of onset
	Tendency towards cutaneous infections (especially *Staph. Aureus* and *Herpes simplex*)/impaired cell-mediated immunity
	Tendency towards non-specific hand or foot dermatitis
	Nipple eczema
	Cheilitis
	Recurrent conjunctivitis
	Dennie-Morgan infraorbital fold
	Keratoconus
	Anterior subcapsular cataracts
	Orbital darkening
	Facial pallor/facial erythema
	Pityriasis alba
	Anterior neck folds
	Itch when sweating
	Intolerance to wool and lipid solvents
	Perifollicular accentuation
	Food intolerance
	Course influenced by environmental/emotional factors
	White dermographism/delayed blanch

with constrains 'objectivity' ('objective' and laboratory tests) and a model with constrains 'simplicity' with only 'objective' features.

After calculation, 13 features were considered the most important in distinguishing AD patients from controls: white dermographism, dyshidrosis of the hands, itch when sweating (itchy skin condition of uninvolved skin when warmed), keratosis pilaris, perlèche (rhagades, erythema or dermatitis at the angels of the mouth), pityriasis alba, wool intolerance, xerosis (dry skin), Hertoghe's sign, Dennie–Morgan folds, palmar hyperlinearity, total serum-IgE and SPT to common allergens. It is remarkable that anamnestic features like a personal or family history of atopic diatheses were not 'strong enough'- or too non-disease-specific, to enter the final criteria.

To avoid 'over optimism' and prove reproducibility a validation study was then performed in 106 cases and 223 dermatological patients (age of participants not given), who served as controls.

'Itch when sweating' as the only feature, obtained 3 points, whereas dry skin –xerosis, and total serum-IgE >150 U/mL yielded 2 points. Remaining features gave 1 atopic point. The authors qualified 10 points for AD diagnosis, and with <3 points a diagnosis of AD was unlikely. The validation study of the three models provided sensitivities of 83–88% and specificities between 84–87% and demonstrated that the sole use of the 'objective' features in the 'simplicity model' provided as good results (sensibility 88%, specificity 84%) as the other models.

One can identify issues of criticism from this study, like the rather weak definitions of the investigated features and the definition of AD patients – 'relapsing flexural eczema'. This definition offers no possibility of investigating this feature by itself, but can also be questioned in terms of other dermatoses with flexural involvement as a symptom, and what about the few AD patients without flexural eczema, how will they perform in such a scoring system?

What history taught us

Hippocrates observed a relationship between allergies, genetic factors and chronic pruritic conditions. These conditions, consistent with AD coined in 1933, have had different titles over time, all describing polymorphous pruritic conditions with personal and/or family tendency to internal manifestations.

Reviewing the different criteria over time revealed that the first well recognized criteria, the 1980 Hanifin & Rajka criteria, were developed empirically on 'clinical experience' and consensus between experts. These criteria, complete but minimally validated, are the most widely used in AD research. In daily clinical setting, it appears to be unrealistic and irrelevant to utilize such comprehensive criteria in patients suspected with AD, but remains an important tool when a detailed examination is demanded, in case of doubt or atypical disease presentation.

Multiple attempts to better diagnose AD have been published. The most common major feature in most criteria is pruritus followed by typical dermatitis distribution and a tendency to a chronic relapsing course. Two criteria (Hanifin & Rajka and Kang & Tian)[6,32] also consider personal/family history of atopic diseases as a major feature, whereas the Millennium criteria are unique in their proposal of allergen-specific serum-IgE or SPT as a mandatory criterion.

Besides these major or basic features, other observations reviewing historical AD studies are observations of tendency to sensitiveness as IgE – total or specific, in the blood or positive SPT's – that seems to be dynamic over time. Eruptions, presented by a wide variety of morphes, xerosis and a range of ill-defined atopic stigmata, also seem to be recurrent in history.

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As earlier shown, AD is a heterogeneous disease with a broad variety of manifestations, cf. Hanifin & Rajka diagnostic criteria.[6] Early pioneers like Hill & Sulzberger[17] observed pooling of AD characteristics that seemed to track together forming AD clinical sub- or phenotypes. For example, they observed a distinct disease pattern which depended on disease (early vs. late) onset, AD with or without presence of elevated specific/total IgE, ACD /sensitization or presence of other atopic diseases, which still are highly investigated.[46–50]

Within the last decade, research in asthma has progressed from a focus on phenotypes towards endotypes, defined as distinct disease entities defined by specific genetic and pathobiological mechanisms linked to the clinical phenotypes, providing enhanced understanding of disease mechanisms,[51,52] possibly ultimately leading to better management and targeted treatment possibilities. In current AD research, possible distinct AD endotypes have also appeared, as e.g. the filaggrin mutated AD patient's combination of a severe course, with an early onset, a high prevalence of sensitization to aeroallergens and other atopic diatheses,[4,53,54] whereas filaggrin mutations do not seem to be associated with AD that has a late onset.[55] Likely, a future diagnostic classification into AD endotypes, or even broader – atopic endotypes, is realistic, but at this point premature.

All current criteria appear to determine AD qualitatively as a uniform disease. A unique example of criteria not following this trend derives from the 1996 Diepgen criteria,[34] suggesting a scoring system referring to the importance of the different atopic features and contemporary laboratory tests. As we further explore in the remainder of this article, this type of, in history unique, scoring system criteria may allow a future creation of a quantitative scale of the AD diagnosis by evaluating the importance of various atopic features, anamnestic, subjective and objective along with the 'new' atopic biomarkers in discriminating AD patients from unaffected individuals.

Since the Hanifin and Rajka era, our understanding of AD pathogenesis has improved dramatically and furthermore, new laboratory and instrumental methods have been developed.

Other quantification studies of atopic dermatitis

Prior to Diepgen's 1996 criteria,[34] two other quantitative studies on AD features, consisting of the Svensson and Diepgen's groups 1980s case–control studies[56,57] have been conducted. Table 6 overviews these along with details on the Diepgen's 1996 criteria.

The authors documented that major features from the Hanifin & Rajka criteria, like personal or family history of atopic diseases were, in fact, not unique for AD patients compared to controls, while minor criteria as dry skin, itch when sweating, intolerance to wool and an elevated total serum-IgE represented more frequent and disease-specific AD features. In Diepgen's first study,[57] three of four basic Hanifin & Rajka criteria only reached 1 of 3 potential points. The proposed scoring systems provided good separation between cases and controls, even in Diepgen's validation study with dermatological patients as controls.[34] Notably, within the atopic group,[57] they found distinct groups of which measured IgE levels corresponded significantly to their level of atopic points. Figure 1 adapted from the Diepgen study demonstrates this phenomenon.

The studies represent an excellent demonstration of a pragmatic approach to a quantitative diagnostic AD scoring system. Limitations of these studies include: first, Svensson and Diepgen's first study[56,57] compared AD patients from a hospital setting with a normal population without dermatological disease, which likely provided a clearer and easier separation between patients and controls. Second, relatively weak or imprecise definitions of the investigated features were given. A final point of question is the AD inclusion criterion: recurrent flexural and lichenified eczema. Since AD patients without this symptom were excluded, the importance of this feature by itself could not be analyzed.

Exploration of new diagnostic criteria for atopic dermatitis

We humbly suggest that instead of previously utilized qualitative criteria; the framework of a new set of diagnostic criteria could be based on the principle of the Diepgen and Svensson works, i.e. a quantitative scoring system. Below we provide published knowledge for some of the current strongest AD features that may be used in a future diagnostic scoring system to better identify affected individuals. Moreover, we discuss available test methods that may possibly be utilized to identify, investigate and quantify current and future AD features.

Quantification of itch – a cardinal subjective atopic feature

As noted earlier, itch seems the cardinal symptom of AD. Atopic itch often begins without visible lesions[58] and is non-responsive to antihistamines.[59] Recently,[60] a significant and inverse correlation was observed between pruritus in AD and quality of life. Patients with symptoms suggesting depression had the most intense itching, confirming the atopic itch's high impact on quality of life.

Attempts to perform objective measurements comprising recording of nocturnal movements like wrist-worn accelerometers/actigraphs, video/infrared video and sound detectors[61–64] have proven insufficient in replicating the patients' subjective experiences by the visual analogue scale (VAS).[65] Conversely, the use of VAS solely as measurement of atopic itch appears inadequate because of the influence of qualitative factors on quantitative scales –already well-known in pain research.[58] Hence, no objective instrumental tool to measure itch is currently available.

The so-called 'atopic itch' has been described via the comprehensive multicomponent questionnaire, the Eppendorf Itch Questionnaire (EIQ), analogous to the McGill pain questionnaire.[66,67] Use of the EIQ demonstrates interesting differences

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Table 6 Three quantitative studies based on anamnestic, subjective and objective features along with laboratory tests

Study group	Svensson *et al.* (1985)[56]	Diepgen *et al.* (1989)[57]	Diepgen *et al.* (1996)[34]
Aim	To quantify atopic symptoms and signs in established AD cases	AD features studied with regard to their diagnostic importance	Develop and validate a objective diagnostic scores of atopic skin disease
Study design	Cross sectional case–control study. Non-blinded	Cross sectional case–control. No information on blinding	2 separate cross sectional case–control studies. Investigators not blinded to AD status 1st study: 3 models of criteria made via backward elimination: objective + laboratory + subjective, objective + laboratory and only objective 2nd: Validation study
Study population	47 AD patients from outpatient clinic 47 controls: dermatological patients without eczema. Age and sex matched Both groups: mean age 23 years	110 AD patients (in and outpatient clinics) median age 21 years 527 controls from normal population Median age 23 years	1st study: 345 AD patients, 618 controls (without skin disease) 2nd: 106 AD patients and 223 controls with other dermatological conditions
AD-cases definition	Recurrent flexural and lichenified eczema	Recurrent flexural itching and lichenified eczema	Relapses of flexural eczema. At least 3 relapses were seen as the gold standard
Method of atopic score system	Chi-square values between groups calculated and utilized to group the atopic symptoms and signs	Chi-square values and relative risk between groups calculated Score system based on chi-square values of only clinical features (no laboratory tests were included) present in >20% of the AD patients	Chi-square values and the regression coefficients β (representing the influence of the various features of AD) between groups calculated Score system based on β estimate values
Findings	3 points ($p < 0.001$): Seasonal variation, xerosis, disorientation by psychological tensions, itch when sweating, total serum IgE > 80 kU/L, personal history of allergic rhinitis, family history of allergic rhinitis, irritation from textiles, hand eczema in childhood, family history of AD 2 points ($p < 0.01$): Facial pallor/erythema, lichenified eczematous knuckle dermatitis, personal history of asthma, keratosis pilaris, food intolerance, nummular eczematous patches, nipple eczema 1 point ($p < 0.05$): Pompholyx, ichthyosis, Dennie-Morgan fold, white reaction on tetrahydrofurfurylnicotinate	3 points ($\chi^2 > 150$): Itch when sweating, intolerance to wool, xerosis, white dermographism, Hertoghe's sign 2 points ($100 < \chi^2 < 150$): AD of the scalp, perlèche, cheilitis, hyperlinear palms, pityriasis alba 1 point ($\chi^2 < 100$): family history of atopy, rhinitis, conjuntivitis, asthma, dyshidrosis, Dennie-Morgan fold, nickel sensitivity, food intolerance, facial erythema,light sensitivity, keratosis pilaris	Validation study: 3 points ($\beta > 2.5$): Itch when sweating, 2 points($1.5 < \beta < 2.5$): xerosis, total serum-IgE > 150 U/mL 1 point ($\beta < 1.5$): perlèche, white dermographism, dyshidrosis/ pompholyx, Hertoghe's sign,wool intolerance, keratosis pilaris, pityriasis alba, Dennie-Morgan fold, palmer hyperlinearity, positive RAST for screening inhalant allergy
Outcome and comments	Cut-off for considered atopic: 14 or 15 points Good discrimination between cases and controls: 15 points caught 96% of the AD patients Authors noted that the controls that obtained many atopic points probably were atopics who have not sought medical attendance	>10 points considered atopic, 6–10 points suspected atopic. The summarized atopic points normal distributed in AD patients (see Fig. 1) Different degrees of atopic severity based on the amount of atopic points were observed Significant IgE increase in the atopic groups, but not in the normal population	>10 points: AD <3 points: probability of AD very small

AD, atopic dermatitis; RAST, radioallergosorbent test.

between characteristics of pruritus in AD and chronic urticaria patients, also suffering from intense pruritus.[58] Even though patients presented with similar pruritus intensity measured by VAS, a much higher EIQ value was observed in AD patients.

Further characterization of itch as a symptom of discomfort when, for example, an atopic individual is exposed to wool or experience itch of unaffected skin when sweating, along importantly with the likely differences to itch experienced in other pruritic diseases could further be investigated objectively by double-blinded challenges with itch and sweat-provoking factors like acetylcholine or capsaicin, with patients using the VAS scale to grade the response. Recently, characterization of the cerebral responses to itch provocation in AD patients, using functional magnetic resonance imaging (fMRI) also have shown interesting results.[68]

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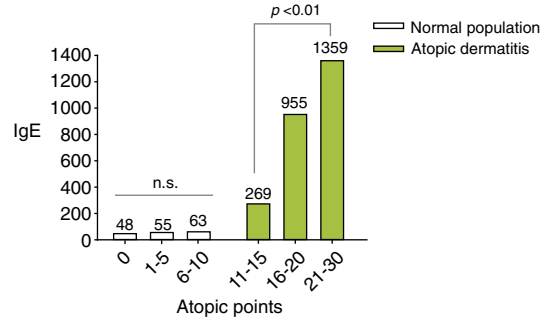

Figure 1 Results of Diepgen's quantitative study from 1989, showing good distribution of'atopic points' between atopic dermatitis patients and controls. Noteworthy is also the significant correlation of total serum IgE in the atopic groups. Adapted from Diepgen *et al.*[57]

Quantifying objective features

Xerosis The important objective feature of atopic dry skin (xerosis) is, according to many studies,[32,33,54,69–71] frequently present in AD. In 1985 Werner and Lindberg,[72] one of the first to investigate and compare AD skin with and without visible dry skin to non-AD skin by trans-epidermal water loss (TEWL), concluded: 'The result of the study may indicate a primary defect in the epidermal barrier: the stratum corneum'. Later studies comparing xerotic AD skin to AD lesions and again to other diseases, utilizing non-invasive biophysical instruments, confirmed a decrease in hydration and an impaired skin barrier function with TEWL increase, but also elevated pH-values and increased stratum corneum cell turn over in AD correlating with clinical xerosis.[72–75]

With the discovery of the multiple functions of profilaggrin, filaggrin and its amino acids as crucial epidermal factors, it becomes clear that atopic xerosis probably either is 'primarily', caused by filaggrin null-mutations, or 'secondary' caused by acquired filaggrin deficiency due to the chronic inflammation and/or exogenous stressors of the skin as filaggrin insufficiency is seen in all AD patients, both in lesional and non-lesional skin, regardless of their genetic status.[25,76]

Studies on biomarkers of filaggrin metabolites by tape stripping represent a possible future non-invasive tool for investigating and comparing AD xerosis to other types of xerosis, e.g. childhood type, of which differentiation from AD is applicable. Natural moisturizing factor (NMF) components, partly generated by filaggrin degradation, provide important stratum corneum water retention and can thereby possibly indirectly serve as a quantitative xerosis measurement.[77,78] Notably, dose-dependent correlations between decreased amount of NMF, filaggrin genotypes and AD severity have been observed.[78]

Atopic stigmata and other objective features Some historical atopic stigmata as palmar hyperlinearity, keratosis pilaris, infraorbital fold (Dennie-Morgan), orbital darkening, facial pallor/erythema, anterior neck folds and perifollicular accentuation, included in the Hanifin and Rajka diagnostic criteria, have been rejected in newer AD criteria because of poor between-observer reproductively.[33,34] Along with other AD stigmata and objective features that have been discussed over time, e.g. Hertoghe's sign (thinning of the lateral part of eyebrow) and perlèche (rhagades, erythema and painful dermatitis at the angles of the mouth), the AD stigmata remain worth investigating and likely include in future criteria, as they, in multiple previous cross-sectional studies,[34,54,79] have demonstrated good discrimination between atopics and controls. Although providing acceptable discrimination, there are great variations in the prevalence of various features among these studies.[31] This is, as explored recently by Deleuran and Vestergaard,[80] probably because these signs change over time, varies with genotype, ethnicities and gender, which make cross-sectional and questionnaire studies less useful to identify these 'intra- and interpatient-variations'.

To further study impact and possible use in diagnostic criteria of objective AD features, including the influence of age of onset, difference within ethnicities, role of gender, different human regional variation like AD of the flexures, hands, feet and face/eyelids, possible distinct atopic morphology, but also importance of personal/family history of atopic diatheses like asthma, allergic rhinitis and food allergies, preferably, confirmed by, e.g. SPT, specific IgE, spirometry and double-blinded food challenges, long-term international observational studies from birth to as long as possible provide the ideal study design.

Although studies exploring AD longitudinally in various age groups exist; these are, unfortunately, most commonly short-term in nature –hence will infrequently provide insight in the long-term complexity of AD's biologic variations.

Examples with longer follow-up time and a large number of patients worth mentioning are The National Child Development Study[81] and the Isle of Wight 1989 birth cohort study[82] – follow-up time of 18 and 23 years respectively. Both used questionnaires, completed by health providers, parents or patients as the investigation method. Williams and Stranchen[81] suggested the importance of long-term studies, as their study,[81] among others,[83] indicated that long-time prognosis of childhood eczema may be worse than short course studies predicted, as they may not catch late childhood or adult relapses. Rystedt *et al.*,[84] Wüthrich *et al.*[85] and Lammintausta *et al.*[86] confirmed these assumptions by reporting AD persistence rates of 40–91% in their >20 year follow-up studies of smaller cohorts of AD patients affiliated to dermatological departments, possibly over representing more severe AD cases.

Another exception to the exciting longitudinal studies, is that of Halkjaer and colleagues from 2006[87] and the follow-up in 2012.[4] Every 6 months, at dermatitis flares or other disease pre-

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sentation, they physically examined a high-risk birth cohort from asthma mothers during the first seven life years to explore predilection sites, progression and AD severity. The latter also including filaggrin gene mutation status, describing distinctive clinical patterns,[4] with tendency towards dermatitis at anatomical sites, e.g. dorsum of hands and cheeks, exposed to drying conditions (coldness, wind or heating), higher frequency of acute dermatitis episodes and more generalized/severe dermatitis compared to the wild type. Other recent studies[53,88] confirm a distinct clinical phenotype in AD patients with filaggrin mutations, probably representing a distinct atopic endotype. As mentioned earlier, at present, we have insufficient knowledge into this complexity to perform a classification into endotypes.

Impact of heritability in risk of AD

Twin studies document strong genetic influence in AD and other atopic diatheses. A 1972 questionnaire study[89] in almost 7000 pairs of adult twins revealed almost 4 times greater AD concordance in monozygotic twins, compared to dizygotic. Another twin study[90] of AD concordance by Schultz-Larsen *et al.* performed as a partial questionnaire and clinical study in 592 twin pairs demonstrated a risk of concordant AD of 86% vs. 21% in, respectively, monozygotic and dizygotic twins. A more recent questionnaire study[91] from Denmark in 11 515 twin pairs, showed concordance rates of 57% (monozygotic twins) vs. 21% (dizygotic twins) and a sevenfold increased risk (monozygotic) of AD compared to threefold increased risk (dizygotic) of AD if an affected twin.

Other studies have likewise demonstrated strong genetic predisposition when investigating influence of parents atopic diseases and AD risk in their offspring[46,92–96] with tendency of AD of parents, followed by asthma and allergic rhinitis, as the most important AD predispositions, whereas the maternal vs. paternal influence does not demonstrate a clear pattern, but likely the maternal influence is the most important.

While previous studies have rejected or reduced the role of inheritance as a diagnostic criterion for AD, e.g. Diepgen *et al.*,[34] genetic predisposition should probably be included in future AD diagnostic criteria as recently highlighted in the aforementioned filaggrin mutation studies. Remember, that the AD epidemic is relatively recent and that the role of genetic predisposition therefore could have been underestimated in early studies on the first generations[1].

Putative future biomarkers for the diagnosis of atopic dermatitis

Sensitization Since discovery of the immunological sensitization phenomena of atopy, many have studied the roles of total and allergic specific IgE antibodies, measured directly in serum and indirectly by performing SPT, against common food and aero-allergens in AD. Through history, it has been discussed whether atopic diathesis is driven by an abnormal T helper 2-lymphocyte response resulting in IgE dysregulation, or if it is simply a pathogenesis cofactor. Recently, it has even been suggested that elevated IgE could be an epiphenomen[97] due to severe inflammation.

Sensitization is, as mentioned earlier, utilized in Bos and colleagues' Millennium criteria[31] from 1998. They are the only criteria suggesting that allergen-specific IgE in serum or positive SPT to 'a reasonable panel' as a mandatory AD criterion. Diepgen *et al.* also investigated the use of IgE in diagnostic criteria[34,57]; total IgE (>100 IU/mL) and specific IgE to common aerosols were, as mentioned, significantly associated with AD, but the latter and largest study[34] showed no significant change in sensitivity or specificity of the diagnostic criteria suggested when serum-IgE measurements was excluded.

In a 2003 review,[98] the prevalence of sensitization in AD patients, defined as positive SPT or the presence of serum IgE antibodies to common environmental allergens, ranged between 47–75% in hospital-based settings and 7–78% in population-based settings.

In a well-performed prospective study from Japan[99]; school children underwent physical examination and laboratory tests annually for 9 years. Levels of total and dust mite-specific serum IgE were significantly stepwise increasing when comparing healthy skin vs. dry skin without AD vs. clinical AD. They documented higher IgE levels in AD patients without improvement during AD in childhood, compared to the AD patients with improvement. These findings are consistent with Diepgen's[57] finding that the more 'atopic points' the more elevated total IgE, suggesting a connection between atopic sensitization, atopic diathesis, severity, and a poorer prognosis. Flohr *et al.*[98] also alluded to this in their review article along with a recent study[100] documenting evident correlation between AD severity, measured by SCORAD[101] and respectively total IgE in children and adults and specific IgE for Malassezia species in children.

Like Hill and Sulzberger's classical paper from 1935,[17] Flohr[98] further explored the number and nature of positive SPT and serum total and specific serum IgE's differ within the same individual over time. Studies seeking to investigate these specific patterns of sensitization during life have indicated the existence of a least one distinct possibly IgE-driven pheno- or even possibly endotype comprising persistent atopic diathesis.[83,102,103] Another study from Flohr and the ISAAC study group physically examined for flexural eczema and skin prick tested more than 28 000 children in 20 countries. The cross-sectional study demonstrated interestingly that the sensitization not was associated with flexural eczema in some parts of the world depending on gross national income.

As discussed, the mentioned studies indicate that total and/or specific IgE may have eligibility to play a role as an AD biomarker, as there may to be a connection between elevated IgE levels

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and AD severity, but its role in distinguishing AD patients from normal population is currently not sufficiently investigated.

Filaggrin mull mutations – our current strongest AD biomarker? Discovery of filaggrin gene mutations, carried by 5–10% of individuals with Northern European and Asian origin, offered a major breakthrough in understanding of epidermal barrier defects as a driver of not only AD, but also likely respiratory atopic disease[2,104] and food allergy.[105] Filaggrin mutations are a major predisposing factor for AD with an overall odds-ratio risk of 3.12–4.78[106] placing filaggrin mutations as a strong biomarker of AD and supporting AD being a very heritable condition.

Thymic stromal lymphopoietin Thymic stromal erythropoietin (TSLP) released by keratinocytes, as a part of the innate inflammatory response promotes differentiation of naïve T-lymphocytes into Th2-lymphocytes, is possibly activated because of filaggrin deficiency caused by an elevation of skin pH, activation of proteases and IL-1.[25] Increased TSLP expression caused by variants in genes coding for TSLP has shown strong association with AD and atopic diatheses.[107,108]

While genetic variants in the TSLP gene and cytokine measurements in serum are not yet reliable,[107] hence premature as AD biomarkers, tape strip analyses may prove valuable in the near future: in a study by Sano *et al.*,[109] the levels of stratum corneum TSLP, measured by a combination of non-invasive immune-staining and tape stripping methods, correlated with SCORAD and epidermal barrier status (especially dry skin score and stratum corneum hydration) in AD patients, even elevated in unaffected skin, compared to healthy controls.

Additional possible biomarkers Serum thymus and activation-regulated chemokine,[110] cutaneous T cell–attracting chemokine (CTACK) levels,[111] serum periostin levels,[112] serum LDH levels,[110,112] serum vitamin D levels,[113,114]serum and mean hair zinc levels,[115,116] absolute serum eosinophil count (AEC),[110,112,117,118] interleukin 18 by tape stripping,[119] blood or tissue interleukin 31,[110,120] among others are other examples of possible AD biomarkers that may be able to discriminate AD patients and normal population and could be included in future criteria.

A future quantitative diagnostic scoring system?

At this point, it is premature to suggest a definite diagnostic quantitative scoring system based on current evidence. However, we humbly suggest that the framework could be based on a scoring system like Diepgen's, where the most important and sensitive features in discriminating the AD individual from normal population would add 'more points', influence, to a final diagnosis compared to other less important features. Then, as a simplified illustrated in Fig. 2, the total number of 'AD points' would translate into a likelihood of AD, e.g. 'not, possible, likely or definite AD'. This sort of diagnostic scoring system is applied in rheumatoid arthritis.[121]

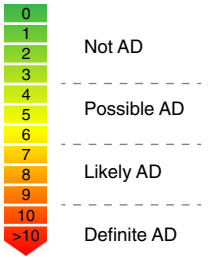

Figure 2 A simplified framework of a quantitative scale graduated into not, possible, likely and definite atopic dermatitis.

Table 7 Suggestion of possible strong/valuable atopic features, that should be further investigated by international cooperation, to be included in new atopic criteria if found important

Feature studied	Putative study design
Subjective:	
Itch	Blinded challenge + VAS, multicomponent questionnaire, fMRI
Objective:	
Measurement of skin barrier function and xerosis	Non-invasive biophysical measurements of, e.g. hydration (conductance), TEWL, lipid composition etc. Tape stripping measurement of amino acids, e.g. filaggrin metabolites, e.g. NMF and cytokines, e.g. TSLP
Atopic stigmata, other objective signs Characterization of morphology and regional variation Role of age, gender, ethnicities	Long-term observational objective study leading to international agreement about the characteristics of features, e.g. age, gender, ethnicity and atopy
Paraclinical (biomarkers):	
Total and specific serum-IgE and skin prick test	Long-term observational objective study with IgE serum levels and/or skin prick test
AD biomarkers as filaggrin mutation status, TSLP, vitamin D, zinc level, eosinophils, TARC, CTACK, periostin, IL 18, IL 31. . .	Long-term observational objective study including laboratory measurements of serum levels and tissue biopsies
Heredity and other atopic diatheses:	
Personal/family history of atopy	Long-term observational objective study
Asthma, rhino-conjunctivitis, food allergy	Long-term observational objective study including blinded lung and food challenges

VAS, visual analog scale; fMRI, functional magnetic resonance imaging; TEWL, transepidermal water loss; NMF, natural moisturizing factor; TSLP, thymic stromal erythropoietin; TARC, thymus and activation-regulated chemokine.

As earlier discussed and summarized in Table 7, subjective and objective atopic features should be further investigated mechanical and intervention wise complemented with interna-

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tional long-term observational studies investigating AD from the cradle to the grave, including investigation of the value of various biomarkers and the connection with the other atopic diatheses, possibly giving insight into the underlying pathogenetic mechanism(s) in AD. Studies should further confirm, reject and hopefully improve the content of future scoring system along with the important question whether such a scoring system would embrace all ages and ethnicities or if a more dynamic score system is needed.

We believe that by investigating AD and atopy by specific knowledge of what differentiates the atopic individual from normal will greatly improve AD research.

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