Biomarkers in atopic dermatitis—a review on behalf of the International Eczema Council

Yael Renert-Yuval, MD,[a] Jacob P. Thyssen, MD, PhD,[b] Robert Bissonnette, MD,[c] Thomas Bieber, MD, PhD,[d] Kenji Kabashima, MD, PhD,[e] DirkJan Hijnen, MD, PhD,[f]* and Emma Guttman-Yassky, MD, PhD[g]*   *New York, NY; Copenhagen, Denmark; Montreal, Quebec, Canada; Bonn, Germany; Kyoto, Japan; and Rotterdam, The Netherlands*

Atopic dermatitis (AD) is a common yet complex skin disease, posing a therapeutic challenge with increasingly recognized different phenotypes among variable patient populations. Because therapeutic response may vary on the basis of heterogeneous clinical and molecular phenotypes, a shift toward precision medicine approaches may improve AD management. Herein, we will consider biomarkers as potential instruments in the toolbox of precision medicine in AD and will review the process of biomarker development and validation, the opinion of AD experts on the use of biomarkers, types of biomarkers, encompassing biomarkers that may improve AD diagnosis, biomarkers reflecting disease severity, and those potentially predicting AD development, concomitant atopic diseases, or therapeutic response, and current practice of biomarkers in AD. We found that chemokine C-C motif ligand 17/thymus and activation-regulated chemokine, a chemoattractant of T_H2 cells, has currently the greatest evidence for robust correlation with AD clinical severity, at both baseline and during therapy, by using the recommendations, assessment, development, and evaluation approach. Although the potential of biomarkers in AD is yet to be fully elucidated, due to the complexity of the disease, a comprehensive approach taking into account both clinical and reliable, AD-specific biomarker evaluations would further facilitate AD research and improve patient management. (J Allergy Clin Immunol 2021;■■■:■■■-■■■.)

Key words: *Atopic dermatitis, biomarker, International Eczema Council, CCL17/TARC, IgE, eosinophils, CCL22/MDC, CCL26/eotaxin-3, CCL27/CTACK, CCL18/pulmonary and activation-regulated chemokine, IL-13, IL-22*

Atopic dermatitis (AD) is a complex disorder in which gene-gene and gene-environment interactions contribute to generate a highly heterogeneous clinical phenotype.[1] This heterogeneity likely reflects yet-to-be-defined mechanisms, coupled with clinical relevance we are only beginning to grasp. Progress in our understanding of the role of microbiome, epidermal barrier function, and different cytokines and other immune mediators underlying the chronic AD inflammation has led to an unprecedented number of new compounds in clinical development, for both the topical and systemic therapy of AD.[2] However, thus far none of the therapeutic approaches can be considered a magic bullet, or a "one-size-fits-all" agent. When using stringent end points such as percent of patients reaching investigator's global assessment 0/1 with a 2-grade decrease or Eczema Area and Severity Index-90 in a monotherapy study design (ie, without adding topical/systemic anti-inflammatory medications), it appears that both biologics that specifically target cytokines or their receptors and broad-acting Janus kinase inhibitors fail to fully control AD in most patients.[3-6] Hence, particularly considering the complexity of AD, there is a need to shift toward precision medicine approaches to improve AD management.

BIOMARKERS: DEFINITION, SUBTYPES, AND OTHER REGULATORY ASPECTS

Biomarkers have always existed for different purposes in medicine, principally as a diagnostic tool. However, AD diagnosis and treatment, as opposed to many other chronic diseases, relies completely on clinical scores rather than biochemical markers. Thus, a reliable biomarker will reduce observatory differences. Herein, we will consider biomarkers as potential instruments in the toolbox of precision medicine in AD. Biomarkers may have tremendous implications in prevention strategies and, most importantly, in strategies used for the development of upcoming new compounds on the background of stringent regulatory landscapes. In this regard, the definition of a biomarker given by regulatory organizations is particularly helpful but obviously not universal. The Food and Drug Administration (FDA) has adopted a rather broad definition: "A defined characteristic that is measured as an indicator of normal biologic processes, pathogenic processes, or responses to an exposure or

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Abbreviations used

AD:	Atopic dermatitis
CCL:	Chemokine C-C motif ligand
CTACK:	Cutaneous T-cell–attracting chemokine
FDA:	Food and Drug Administration
FLG:	Filaggrin
GRADE:	Grading of Recommendations, Assessment, Development, and Evaluation
IEC:	International Eczema Council
MDC:	Macrophage-derived chemokine
TARC:	Thymus and activation-regulated chemokine

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intervention, including therapeutic interventions." The FDA also adds the following comment: "Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives." Interestingly, the European Medicines Agency has another, more restrictive definition: "A biological molecule found in blood, other body fluids, or tissues that can be used to follow body processes and diseases in humans and animals."

In the process of biomarker discovery, one should distinguish between the kind of biologic material (or its origin) on one hand and the purpose/value of the biomarker on the other hand. For the first group, a wide range of biologic material can be used such as (1) genomic information (eg, specific gene sequences or epigenetic modification of genes), (2) transcriptomic profiles obtained by analysis of mRNA and miRNA, (3) proteins such as cytokines and other mediators from body fluids (whole blood, serum, plasma, tissue fluids) or tape stripping, and (4) morphological information (immunohistochemical staining and pictures thereof).

This is to be distinguished from the purpose/value of biomarkers with 7 different subtypes as defined by the FDA-NIH Biomarker Working Group (www.ncbi.nlm.nih.gov/books/NBK326791/): (1) susceptibility/risk, (2) diagnostic, (3) monitoring/severity, (4) prognostic, (5) predictive, (6) pharmacodynamic/response, and (7) safety. All these subtypes could potentially be of importance in the context of the management of AD.

Unfortunately, the literature and the classical understanding thereof in the scientific community has generated the idea that a biomarker can be easily described and used in the context of disease management. In reality, bringing a given biomarker from discovery to clinical practice and regulatory acceptance in clinical development and/or as a companion diagnostic is a rather complex procedure, widely underestimated by most scientists, which is often comparable to a drug development process. There are several crucial steps in the evolution of a biomarker before it reaches the status of qualification in clinical practice.

In a nutshell, the life of a biomarker starts with its discovery, which can be either by chance or the product of a hypothesis-driven biomarker discovery program based on a patient registry collecting high-quality phenotypical data linked to a biobank with several hundreds of specimens from these patients. The next step is a first (internal) analytical and clinical validation in a limited number of clinical cases. Thereafter, the biomarker must undergo another (external) validation step, ideally from independent institutions, using a large cohort of patients where the reproducibility is key. Once this goal of internal and external validation is reached, the biomarker is subjected to a complex process of regulatory qualification, which is supported by a number of guidance documents from the regulatory agencies (FDA, European Medicines Agency). Thus, developing a newly discovered biomarker to the stage of an accepted companion diagnostic for the management of a disease is a complex and demanding process.

THE GRADING OF RECOMMENDATIONS, ASSESSMENT, DEVELOPMENT, AND EVALUATION APPROACH TO ASSESS EVIDENCE STRENGTH

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach offers a system for rating quality of evidence, with a structured process for developing and presenting evidence summary.[7] Herein, we searched for AD-related publications that included correlation analysis and found a significant ($P < .05$) correlation coefficient of greater than or equal to 0.4 between AD clinical severity and blood/skin potential biomarkers, both at baseline and during various AD treatments, and across both pediatric and adult patients. Biomarkers that were found to robustly correlate with AD clinical severity in more than 3 publications were included in this review. Next, we summarized these findings using the GRADE approach, in which accumulated evidence per each potential biomarker (separated by pediatric and adults, and at baseline and during topical and systemic treatments) was graded on the basis of strength of the overall published data, given our inclusion threshold.

BIOMARKERS IN AD INTERNATIONAL ECZEMA COUNCIL SURVEY RESULTS

The International Eczema Council (IEC) consists of more than 100 councilors and associates (https://www.eczemacouncil.org/), all experts in AD. Before the IEC meeting at the Society of Investigative Dermatology meeting in 2019 in Chicago, an invitation to an internet-based survey on biomarkers for AD was sent by email to all IEC councilors and associates to examine their opinion regarding biomarkers in AD (Table I; for detailed questions, see this article's Online Repository at www.jacionline.org). Monkey survey software was used for data collection. Overall, the experts believe AD is a heterogeneous disease with at least 3 different phenotypes, that biomarkers may help to stratify patients by phenotypes and improve patient management and treatment compliance, and that future developments should focus on their use as predictors of therapeutic response.

TYPES OF BIOMARKERS IN AD

Potential biomarkers may be subdivided on the basis of their suggested use.

Biomarkers differentiating AD from psoriasis

Some biomarkers seem to reliably distinguish between AD and psoriasis (namely NOS2 and chemokine C-C motif ligand [CCL] 27/cutaneous T-cell–attracting chemokine [CTACK]),[8-10] thus potentially improving the diagnosis and management of patients with psoriasiform dermatitis (Table II).

TABLE I. Results of the biomarkers survey by IEC AD experts

Question	Yes (N)	No (N)	Follow-up questions (N)
Do you think that AD is a heterogeneous disease?	97.52% (41)	2.38% (1)	How many different AD phenotypes are there? (38) ● >3 types of different AD phenotypes (92.7%) ● <3 (7.3%) How would you stratify AD phenotypes? (38) ● Combining clinical features and biomarkers (92.7%) ● Only clinical features (7.3%) Which groups of biomarkers should be used for patients' stratification? (36) ● Blood biomarkers (70%) ● Skin biomarkers (genomics/transcriptomics) (50%) ● Proteomics (28%) ● Genomics and transcriptomics in tape-strips (28%) ● Physiological properties (eg, TEWL and Raman spectroscopy) (25%)
Are you using blood tests/biomarkers for the diagnosis of AD?	29.55% (13)	70.45% (31)	Which are you using? (13) ● IgE (100%) ● Eosinophils (92.3%) ● Other (FLG, LDH, CCL17/TARC) (30.8%)
Do you think that blood tests/biomarkers are useful for assessing the severity of AD?	59.09% (25)	40.91% (18)	Why not? ● Lack of reliability, validity, and commercial availability Why yes? ● Improve selection of patients for specific therapies or in clinical trials ● Improve comparability of clinical trials ● Allow better follow-up tool in daily practice ● Improve compliance of patients and patient encouragement.
Could blood test/biomarkers be useful for assessing treatment compliance?	76.74% (33)	23.26% (10)	Which biomarkers would you suggest? (17) ● CCL17/TARC (52.9%) ● IgE (47.1%) ● p-EASI (formula containing CCL17/TARC, sIL-2R, IL-22) (35.3%) ● Eosinophils (35.3%) ● IL-13 (23.5%) ● Other markers (CCL22, CCL26, sIL-2R, and IL-22—selected by <23.5%)
How would you prioritize the needs for blood test/biomarkers?			Top-rated development priorities: (40) ● Biomarkers predicting treatment response, either in general, by identification of AD endo/phenotypes to predict treatment response, or by identifying responders to a particular drug before treatment initiation Lower priority for development: ● The use of biomarkers for disease severity, treatment response, diagnosis, and the development of less-invasive biomarkers (all ranked almost equally)

EASI, Eczema Area and Severity Index; *LDH,* lactate dehydrogenase; *TEWL,* transepidermal water loss.

Biomarkers correlating with clinical severity

These include markers related with general inflammation such as serum lactate dehydrogenase,[11-14] C-reactive protein,[11] along with markers related with allergy (eg, peripheral eosinophil counts).[11,12,15-19] Because AD is T_H2/T_H22-centered, cytokines and chemokines related with these immune pathways and correlated with disease severity in untreated or posttreated tissues (either skin or serum) were also investigated as possible biomarkers (Tables III and IV and Fig 1). Such cytokines include the key T_H2 marker IL-13[41,58,59,66,67,95,100] and the key T_H22-related cytokine IL-22.[41,58,59,64,84] T_H2-related chemokines correlated with AD severity include CCL17/thymus and activation-regulated chemokine (TARC),[13,14,20,24,27-33,35-39,94,101-104] CCL26/eosinophil-attracting chemokine (eotaxin-3),[43,58,68,85,91,95,105] CCL27/CTACK,[29,30,33,74,75] CCL18/pulmonary and activation-regulated chemokine,[65,68,83,84] and CCL22/macrophage-derived chemokine (MDC).[26,28,40,44,45,90] Of note, circulating AD-related biomarkers are found in moderate to severe patients, whereas mild patients may not consistently display upregulation of AD-related biomarkers in their serum.[25]

Barrier-related potential biomarkers, including filaggrin (FLG), loricrin, and natural moisturizing factor, may inversely correlate with disease severity.[106]

Because of the complexity of AD pathogenesis, a few reports modeled a combination of biomarkers to better reflect molecular changes correlating with clinical severity.[39,58,107] The current evidence from the literature, including only those reports in which a significant and robust correlation between AD clinical severity and a tissue biomarker was found ($r \geq 0.4$; $P < .05$), is summarized using the GRADE approach in Table V.[7]

Biomarkers that failed to show consistent correlation with severity

Although total serum IgE levels (particularly in extrinsic AD)[11,13,28,49,52-54,56,59,109-111] are elevated in AD, these are not consistently correlated with disease severity or only weakly correlated,[12,51,90,112] and in dupilumab studies, responses of patients with AD are regardless of their baseline IgE levels.[113] Thus, it is likely that IgE is a bystander in AD pathogenesis, rather than a treatment target.[114,115] Although periostin is implicated in the

TABLE II. Biomarkers as disease classifiers, potentially improving diagnosis by differentiating AD and psoriasis

Biomarker	Full name	Functional effect	Abnormalities
NOS2	Inducible nitric oxidase synthase	Catalyzing the production of nitric oxide, a toxic defense molecule against infections, and a regulator of functional activity, growth, and death of immune cells including T cells, antigen-presenting cells, mast cells, neutrophils, and natural killer cells	Upregulated in psoriasis, downregulated in AD
CCL27/CTACK	Chemokine (C-C motif) ligand 27/cutaneous T-cell–attracting chemokine	Expressed by keratinocytes. Mediates the migration of lymphocytes into the skin by binding to CCR10	Upregulated in AD, downregulated in psoriasis

pathogenesis of AD and was suggested as a potential AD biomarker by some reports, evidence for a correlation with disease severity is weak.[18,116,117] Curiously, despite some reports on the correlation of the "itch cytokine," IL-31, with disease severity,[62,118] more evidence is accumulating on the lack of such correlation.[102,119-121]

Predictive biomarkers

Tissue biomarkers predicting disease onset include TARC and IgE in the umbilical cords of newborns[122,123] and natural moisturizing factor levels in neonates' skin,[124] which are known to strongly correlate with transepidermal water loss,[23] another predictor of AD development in newborns.[125,126] Moisturizers can prevent AD in high-risk infants,[127] and were shown to alter skin microbiome and reduce skin pH in this population.[128] Other biomarkers may predict AD persistence (eg, low serum vascular endothelial growth factor [VEGF]).[129]

Because of the heterogeneous nature of AD pathophysiology, AD therapies targeting individual pathways are unlikely to result in high levels of response by all patients with AD,[130,131] as seen in psoriasis with IL-17/IL-23 targeting.[132] Thus, using biomarkers that can identify patient subsets that are more likely to respond to individual drugs or pathway antagonism would be beneficial. AD clinical trials have increasingly incorporated mechanistic analyses to assess potential biomarkers in both skin and blood (Table IV).[96,133,134] Also, as AD symptoms fluctuate over time, biomarkers have the potential to provide objective insights into patient response to treatment and elucidate the mechanism of action of a drug. Biomarkers can either be common to all treatments ("disease response biomarkers") or can be specific to individual treatments ("treatment-specific biomarkers"). For example, data from the phase 2 tralokinumab (IL-13 blocker) trial in AD have identified dipeptidyl peptidase-4 as a potential treatment response biomarker for IL-13 inhibition,[4] and in asthma, periostin was identified as a response biomarker to IL-13 inhibition.[135,136] Another example is the mAb inhibiting IL-22, fezakinumab, to which patients with AD with high IL-22 levels in skin biopsies at baseline were significantly more likely to respond.[133] Other treatment-specific predictive biomarkers include CXCL9 (T_H1/ interferon-related) for cyclosporine and CXCL2 (T_H17-related) for dupilumab.[137] Although broad immune-suppressors (eg, methotrexate or azathioprine) were also studied in AD, no decreases in individual cytokine levels significantly correlated with response across agents.[138]

Recently, CCL22/MDC was found as the best biomarker of disease response across studies using different therapeutics,[137] as baseline CCL22/MDC expression correlated with future clinical improvement across multiple studies at various time points,

including topical treatment (crisaborole), systemic immunosuppressant (cyclosporine), and targeted treatment (fezakinumab).[137]

CCL17/TARC AS A BIOMARKER OF AD

Since CCL17/TARC was introduced to the field, primarily in Japan, it was reported as the most reliable biomarker studied,[15] sensitive to fluctuations in clinical findings.[20,24,27,28,38,101-103] CCL17/TARC is a CC chemokine discovered in 1996 by Imai et al,[139] constitutively expressed in the thymus and a member of the T_H2 chemokine family that attracts CC chemokine receptor 4–positive cells. Of note, thymus size also correlates with AD activity, and thymectomy may reduce the risk of AD.[140,141] T_H2-type cells and related products are significantly upregulated across various AD populations.[43,59,65,142-144] In AD lesional skin, CCL17/TARC is expressed on keratinocytes in the epidermis, vascular endothelial cells, T cells, and dendritic cells.[20,142] In Japan, serum CCL17/TARC levels have been measured commercially under health insurance support since 2008. Currently, after more than a decade of experience in patients with AD, CCL17/TARC has become a useful clinical biomarker for monitoring the efficacy of treatment and for ensuring successful treatment outcomes in the Japanese population.[101]

The normal level of serum CCL17/TARC in healthy adults is less than 450 pg/mL; its level in healthy children differs depending on age.[31] Several investigations have also confirmed a high correlation between the AD severity and serum CCL17/TARC levels in pediatric patients.[27,29,31,33,37] Moreover, increased CCL17/TARC levels from umbilical cord blood may even predict AD in infancy.[122] Reports on the correlations between CCL17/TARC levels in the skin and clinical severity are sparse.[21,25,145]

Monitoring of serum CCL17/TARC levels could also be harnessed as an educational tool, improving patients' adherence to treatment regimens. Patients can view their own disease activity as an objective number, and a rapid fall in the initially high serum CCL17/TARC levels due to adequate treatment can surely enhance compliance, a known pitfall in AD management.[146] Moreover, patients receiving proactive treatment showed decreased but still high serum CCL17/TARC levels and were thus motivated to receive continuous therapy. CCL17/TARC is also reliable for assessing nonvisible/subclinical yet active AD-related inflammation, and high levels of CCL17/TARC may suggest frequent AD relapses even after clinical resolution, where a relatively thorough proactive treatment may be recommended.[35]

Nevertheless, the limitations of CCL17/TARC as an AD biomarker should also be acknowledged. Elevated serum CCL17/TARC level is not specific to AD, and could also be

TABLE III. Potential biomarkers reported to strongly and significantly correlate with clinical severity indices of AD (correlation coefficient ≥0.4, $P < .05$)

Biomarker (no. of publications)	Serum					Skin				
	Author	Lab method	Corr method	Year	Cohort (n)	Author	Lab method	Corr method	Year	Cohort (n)
CCL17/TARC (>20)	Kakinuma et al[20]	E	S	2001	40	Morita et al[21]* (LS-TS)	IF	S	2010	33
	Horikawa et al[22]	E	P	2002	52	McAleer et al[23]† (NL-TS)	ECL	S	2019	66
	Fujisawa et al[24]	E	S	2002	29	He et al[25] (LS-B)	PCR	P	2020	61
	Leung et al[26]†	E	S	2003	20					
	Hijnen et al[27]‡	E	S	2004	177					
	Jahnz-Rozyk et al[28]	E	P	2005	43					
	Song et al[29]†	E	S	2006	157					
	Nakazato et al[30]†	E	S	2008	34					
	Fujisawa et al[31]†	E	S	2009	27					
	van Velsen et al[32]†	E	P/S	2010	60					
	Morita et al[21]	E	S	2010	33					
	Kou et al[13]	E	S	2012	121					
	Machura et al[33]†	E	S	2012	26					
	Furue et al[34]§	E	S	2012	61					
	Mizawa et al[14]	NA	S	2013	30					
	Kataoka[35]‖	NA	NA	2014	96					
	Landheer et al[36]‡	E	S	2014	320					
	Ahrens et al[37]†	E	S	2015	128					
	Gu et al[38]	E	S	2015	73					
	Hulshof et al[39]†	L	S	2018	41					
CCL22/MDC (>10)	Kakinuma et al[40]	E	S	2002	45	Tintle et al[41]	PCR	S	2011	12
	Fujisawa et al[24]	E	S	2002	29	Suarez-Farinas et al[42] (LS/NL-B)	PCR	S	2011	15
	Leung et al[26]†	E	S	2003	20	Wen et al[43] (NL-B)	PCR	P	2018	12
	Jahnz-Rozyk et al[28]	E	P	2005	43					
	Gunther et al[44]	E	P	2005	36					
	Angelova-Fischer et al[45]	E	P	2006	21					
	Hashimoto et al[46]	E¶	NA	2006	11					
	Nakazato et al[30]†	E	S	2008	34					
	Wen et al[43]‖	ECL	P	2018	15					
	Brunner et al[47]†‡	O	S	2019	30					
	McAleer et al[23]†	ECL	S	2019	47					
IgE (>10)	Tsuboi et al[48]#	IRMA	P	1998	17	NA				
	Yoshizawa et al[49]	NA	S	2002	26					
	Kaminishi et al[50]#	FEIA	P	2002	20					
	Jahnz-Rozyk et al[28]	E	P	2005	43					
	Aral et al[51]†	N	S	2006	20					
	Salomon and Baran[52]	E	P/S	2008	49					
	Wu et al[53]†	F	P	2011	48					
	Suarez-Farinas et al[54]	E	P	2013	42					
	Zedan et al[55]†	E	NA	2015	50					
	Glatz et al[56]	E	S	2015	67					
	Rosinska-Wieckowicz et al[57]	F	S	2016	102					
		E	P	2017	25					
	Ungar et al[58]#	E	P	2018	15					
	Wen et al[43]	E	S	2019	15					
	Sanyal et al[59]									
CCL22/MDC (>10)	Kakinuma et al[40]	E	S	2002	45	Tintle et al[41]	PCR	S	2011	12
	Fujisawa et al[24]	E	S	2002	29	Suarez-Farinas et al[42] (LS/NL-B)	PCR	S	2011	15
	Leung et al[26]†	E	S	2003	20	Wen et al[43] (NL-B)	PCR	P	2018	12
	Jahnz-Rozyk et al[28]	E	P	2005	43					
	Gunther et al[44]	E	P	2005	36					
	Angelova-Fischer et al[45]	E	P	2006	21					
	Hashimoto et al[46]	E#	NA	2006	11					
	Nakazato et al[30]†	E	S	2008	34					
	Wen et al[43]‖	ECL	P	2018	15					
	Brunner et al[47]†‡	O	S	2019	30					
	McAleer et al[23]†	ECL	S	2019	47					

(Continued)

TABLE III. *(Continued)*

Biomarker (no. of publications)	Serum					Skin				
	Author	Lab method	Corr method	Year	Cohort (n)	Author	Lab method	Corr method	Year	Cohort (n)
Eosinophils/ECP (>10)	Mukai et al[60]	C	NA	1990	30	NA				
	Czech et al[19]‡	RIA	S	1992	19					
	Kagi et al[16]	RIA	S	1992	37					
	Halmerbauer et al[61]†	RIA	K	1997	20					
	Tsuboi et al[48]	C	P	1998	17					
	Yoshizawa et al[49]	NA	S	2002	26					
	Raap et al[62]†	IC	S	2012	60					
	Kaminishi et al[50]	C	P	2002	20					
	Angelova-Fischer et al[45]	FEIA	P	2006	21					
	Morishima et al[12]	C	S	2010	58					
	Wu et al[53]†	FEIA	P	2011	48					
	Ungar et al[58]	C	P	2017	25					
	Chen et al[63]	NA	S	2019	12					
IL-22 (>5)	Nograles et al[64]	F	LRA	2009	12	Tintle et al[41] (LS-B)‖	PCR	S	2011	12
	Ungar et al[58]	EMD	P	2017	25	Suarez-Farinas et al[42] (LS/NL-B)	PCR	S	2011	12
						Esaki et al[65]†§ (LS-B)	PCR	P	2016	19
						Ungar et al[58] (LS/NL-B)	PCR	P	2017	25
						Wen et al[43] (NL-B)‖	PCR	P	2018	15
						Sanyal et al[59] (LS-B)	PCR	S	2019	15
IL-13 (>5)	Koning et al[66]†	E	S	1997	15	Tintle et al[41] (LS-B)‖	PCR	S	2011	12
	Ungar et al[58]	E	P	2017	25	Suarez-Farinas et al[42] (LS-B)	PCR	S	2011	12
						Szegedi et al[67] (LS-ISF)	L	P/S	2015	16
						Wen et al[43] (NL-B)	PCR	P	2018	15
						Guttman-Yassky et al[68]†** (LS-TS)	PCR	S	2019	21
						Sanyal et al[59] (LS/NL-B)	PCR	S	2019	15
						He et al[25] (LS-B)	PCR	P	2020	61
IL-18 (>5)	Hon et al[69]†	E	S	2004	19	Inoue et al[70] (LS/NL-TS)	E	S	2011	95
	Aral et al[51]†	E	S	2006	20	McAleer et al[23]*† (NL-TS)	ECL	S	2019	66
	Park and Youn[71]	NA	NA	2007	65	Pavel et al[72] (LS-B)	O	S	2020	20
	Kou et al[13]	E	S	2012	121					
	Zedan et al[55]†	E	NA	2015	50					
	Suwarsa et al[73]	E	P	2017	20					
CCL27/CTACK (>5)	Kakinuma et al[74]	E	S	2003	50	—	—	—	—	—
	Hon et al[75]*†	E	S	2004	37					
	Hijnen et al[27]‡	E	S	2004	76					
	Song et al[29]†	E	S	2006	157					
	Nakazato et al[30]†	E	S	2008	34					
	Machura et al[33]†	E	S	2012	26					
S100A7/12 (>5)	—	—	—	—	—	Suarez-Farinas et al[42] (LS-B)	PCR	S	2011	12
						Tintle et al[41] (LS-B)‖	PCR	S	2011	12
						Suarez-Farinas et al[54] (LS-B)	PCR	P	2013	7
						Ungar et al[58] (LS+/NL-B)	PCR	P	2017	25
						Guttman-Yassky et al[68]† (LS-TS)	PCR	S	2019	21
						Sanyal et al[59] (LS-B)	PCR	S	2019	15
						He et al[25] (LS-B)	PCR	P	2020	61
E-selectin (>5)	Morita et al[76]	E	NA	1995	23	—	—	—	—	—
	Yamashita et al[77]	E	K	1997	53					
	Wolkerstorfer et al†[78]	E	S	2003	15					
	Angelova-Fischer et al[45]	E	P	2006	21					
	Brunner et al[79]	O	S	2017	59					
	Brunner et al[47]†‡	O	S	2019	30					
MMP12 (>5)	Brunner et al[79]	O	S	2017	59	Suarez-Farinas et al[42] (LS-B)	PCR	S	2011	12
	Brunner et al[47]†‡	O	S	2019	30	Suarez-Farinas et al[54] (LS-B)	PCR	P	2013	7
	He et al[80]	O	P	2020	71	Ungar et al[58] (NL-B)	PCR	P	2017	25
						Pavel et al[81]†** (NL-TS)	R	S	2020	19
LDH (>5)	Mukai et al[60]	NA	NA	1990	80	NA				
	Tsuboi et al[48]		P	1998	17					
	Morishima et al[12]		S	2010	58					
	Kou et al[13]		S	2012	121					
	Mizawa et al[14]		S	2013	30					
	Kataoka[35]‖		NA	2014	96					
	Olesen et al[82]		S	2019	43					

TABLE III. *(Continued)*

Biomarker (no. of publications)	Serum					Skin				
	Author	Lab method	Corr method	Year	Cohort (n)	Author	Lab method	Corr method	Year	Cohort (n)
CCL18/PARC (≥5)	Hon et al[83]†	E	P	2011	108	Suarez-Farinas et al[42] (NL-B)	PCR	S	2011	12
						Gittler et al[84] (NL-B)	PCR	S	2012	10
						Esaki et al[65]† (LS-B)	PCR	P	2016	19
						Guttman-Yassky et al[68]†** (LS-TS)	PCR	S	2019	21
Eotaxin-3/CCL26 (≥5)	Kagami et al[85]	E	S	2003	30	Zhou et al[86] (LS-B)	PCR	S	2019	27
	Wen et al[43]	ECL	P	2018	15	Guttman-Yassky et al[68]†§‖ (LS-TP)	PCR	S	2019	21
IL-19 (≥5)	Oka et al[87]	E	S	2017	21	Esaki et al[65]† (LS-B)	PCR	P	2016	19
	Konrad et al[88]‖	E	S	2019	124	Guttman-Yassky et al[68]† (LS-TS)‖	PCR	S	2019	21
						Pavel et al[81]†‡ (LS-TS)‖	R	S	2020	19

B, Skin biopsy; *C*, cell count; *Corr*, correlation; *ECP*, eosinophil cationic protein; *E*, ELISA; *ECL*, electrochemiluminescence immunoassay; *EMD*, Erenna immunoassay; *F*, flow cytometry; *FEIA*, fluorescent enzyme immunoassays; *IC*, ImmunoCap system; *IF*, immunofluorescence; *IRMA*, immunoradiometric assay; *ISF*, interstitial fluid; *K*, Kendall rank correlation; *L*, Luminex; *LDH*, lactate dehydrogenase; *LRA*, linear regression analysis; *LS*, lesional; *N*, nephelometric method; *NA*, not applicable/available; *NL*, nonlesional; *O*, OLINK proteomics; *PARC*, pulmonary and activation-regulated chemokine; *R*, RNA-sequencing; *RIA*, ECP radioimmunoassay; *SCORAD*, SCORing of Atopic Dermatitis; *TEWL*, transepidermal water loss; *TS*, tape-strips.

*Correlated with SCORAD components and not with the total SCORAD.

†Pediatric cohort.

‡Correlated with Six Area, Six Sign AD/body surface area/Leicester severity score/scoring system as described by Costa et al.[89]

§Correlated with TEWL.

‖*P* ≤ .1.

¶Performed on monocyte-derived circulating dendritic cells.

#Log2(IgE) was correlated with SCORAD.

**Correlated with pruritus.

found in bullous pemphigoid, scabies, polymorphic prurigo, cutaneous T-cell lymphoma, drug eruption, pustular dermatosis, and other skin diseases,[147-149] as well as in hypereosinophilic syndrome, Hodgkin lymphoma, and other internal disorders.[150,151] Also, some patients with severe AD and patients with nodular prurigo or longstanding severe chronic lichenified lesions occasionally show normal or even low serum CCL17/TARC levels. Such cases may be explained by the heterogeneric pathomechanisms of AD. In addition, the added benefit of CCL17/TARC beyond a surrogate of clinical severity, for example, as a predictor of therapeutic response or as a reliable biomarker for clinical trials, still needs to be validated in future studies, using repeated testing.

AD BIOMARKERS ACROSS DISEASE PHENOTYPES

Two T-cell subsets—T_H2 and T_H22—are commonly activated across AD subtypes, yet specific biomarkers vary among different populations. Some examples of AD subtypes where phenotypic features may be explained by biomarker-related findings follow.

Patients with AD in different ethnicities

The Asian AD phenotype is characterized by greater expression of T_H17-related markers (IL-17A, IL-19, CCL20) along with upregulation of IL-22 and the IL-17/IL-22–induced S100A12 in comparison to European-American patients with AD, but not to the levels found in psoriasis.[43,144,152] This is particularly significant given most Asian patients with AD have extrinsic AD (high IgE levels), which tends to be associated with lower T_H17 expression than intrinsic AD.[144] These data suggest that Asian patients with AD present an immune dysregulation that is between European-American AD and psoriasis, and correlates well with the clinical phenotype of Asian AD, characterized by relatively well demarcated, psoriasiform lesions.[143] Black patients with AD largely lack FLG mutations, in parallel with T_H2/T_H22

predominance and T_H1/T_H17 attenuation.[59] These may contribute to the lower rate of transepidermal water loss in black AD and to the atypical lichenified phenotype commonly seen in black patients with AD, potentially resulting from T_H22 overexpression.[143,153]

Age-related changes in AD

Elderly patients (≥61 years old) with AD present a relative decrease in T_H2/T_H22 biomarkers with parallel increase in T_H1/T_H17 biomarkers, and a less pronounced barrier defect.[86] The latter finding may contribute to the clinical observation of allergic sensitization as part of the atopic march, following AD initiation only at young age, and supports the notion that impaired barrier likely plays a major role in this process.

In addition, early-onset AD in infants is molecularly similar to psoriasis with a relatively dominant T_H17-related skewing,[65] in line with the extensor distribution of lesions in this age group, resembling that of psoriasis.

Biomarkers in association with AD comorbidities

In pediatric patients with AD, KRT5, KRT14, KRT16, FLG breakdown products, and AD clinical severity were predictive of concomitant food allergy.[154] FLG mutations with suppressed levels of FLG expression predispose to AD, but are also associated with other diseases including asthma, irritant and allergic contact dermatitis, and alopecia areata.[155] High levels of IgE and dysfunctional/low levels of FLG may predispose patients with AD to food allergy as part of the atopic march.[156]

Presence of *Staphylococcus aureus* colonization in AD

Finally, patients with AD colonized with *S aureus* have higher levels of type 2 biomarkers (including eosinophils, IgE, CCL17/

TABLE IV. Potential biomarkers reported to strongly and significantly correlate with clinical therapeutic response in AD (correlation coefficient ≥0.4, $P < .05$)

Biomarker (no. of publications)	Serum					Skin				
	Author	Lab method	Corr method	Year	Cohort (n)	Author	Lab method	Corr method	Year	Cohort (n)
CCL17/TARC (>5)	Furukawa et al[90]	E	NA	2004	15	Khattri et al[91] (LS-B, P)	PCR	S	2014	19
	Kwon et al[92]	E	LRA	2010	20	Koppes et al[93] (LS-TS)	E	S	2016	21
	Beck et al[94]*	E	NA	2014	55	Pavel et al[95] (LS-B)	PCR	S	2019	36
	Ungar et al[58]†	ECL	P	2017	25					
MDC/CCL22 (>5)	Furukawa et al[90]	E	NA	2004	15	Khattri et al[91] (LS-B)	PCR	S	2014	19
	Kwon et al[92]	E	LRA	2010	20	Pavel et al[95] (LS-B)	PCR	S	2019	36
						Guttman-Yassky et al[96] (LS-B)†	PCR	S	2019	54
IL-13 (≥5)	Ungar et al[58]	E	P	2017	25	Khattri et al[91] (LS-B)	PCR	S	2014	19
						Ungar et al[58] (LS-B)	PCR	P	2017	25
						Pavel et al[95] (LS-B)	PCR	S	2019	36
						Guttman-Yassky et al[96] (LS-B)†	PCR	S	2019	54
S100A7/8/12 (≥5)	—	—	—	—	—	Tintle et al[41] (LS-B)†	PCR	S	2011	12
						Khattri et al[91] (LS-B)	PCR	S	2014	19
						Pavel et al[95] (LS-B)	PCR	S	2019	36
						Bissonnette et al[97]‡ (LS-B)	PCR	S	2019	40
						Guttman-Yassky et al[96] (LS-B)	PCR	S	2019	54
IL-22 (>3)	—	—	—	—	—	Tintle et al[41] (LS-B)	PCR	S	2011	12
						Khattri et al[91] (LS-B)	PCR	S	2014	19
						Ungar et al[58] (LS/NL-B)	PCR	P	2017	25
						Pavel et al[95] (LS-B)	PCR	S	2019	36
CCL13/MCP-4 (>3)	Ungar et al[58]	ECP	P	2017	25	Hamilton et al[98] (LS-B)†	PCR	P	2014	18
						Ungar et al[58] (NL-B)	PCR	P	2017	25
						Pavel et al[95] (LS-B)	PCR	S	2019	36
						He et al[99] (LS-TS)	O	S	2020	26
Eotaxin-3/CCL26 (≥3)	—	—	—	—	—	Hamilton et al[98] (LS-B)	PCR	P	2014	18
						Khattri et al[91] (LS-B)	PCR	S	2014	19
						Pavel et al[95] (LS-B)	PCR	S	2019	36
CCL18/PARC (≥3)	Guttman-Yassky et al[96]	E	S	2019	54	Khattri et al[91] (LS-B)	PCR	S	2014	19
						Ungar et al[58] (LS/NL-B)	PCR	P	2017	25

B, Skin biopsy; *Corr*, correlation; *E*, ELISA; *ECL*, electrochemiluminescence immunoassay; *LRA*, linear regression analysis; *LS*, lesional; *N*, nephelometric method; *NL*, nonlesional; *PARC*, pulmonary and activation-regulated chemokine; *TS*, tape-strips.

*Correlated with pruritus.

†$P \leq .1$.

‡Correlated with Leicester severity score/Investigator's Static Global Assessment.

TARC, and CCL26/eotaxin-3) and lactate dehydrogenase, along with more severe clinical parameters, including all severity scores, barrier dysfunction (by transepidermal water loss), and greater allergen sensitization.[157]

MINIMALLY INVASIVE BIOMARKERS

Through studies of skin biopsies, biomarkers of the immune milieu and barrier alterations of AD have been defined and facilitated therapeutic development. The inflammatory profile of AD is characterized by T_H2 and T_H22 skewing, with variable T_H1 and T_H17 components, depending on the disease subset (as detailed above).[43,59,143,144] The barrier defects of AD include abnormalities in epidermal differentiation (FLG, loricrin, etc), tight junction (claudins), and lipid products (elongation of very long chain fatty acids-like 3 [ELOVL3], fatty acid 2-hydroxylase [FA2H], etc). Skin biopsies were also instrumental and sensitive in providing useful information on early and late changes with various treatments. Treatment response biomarkers provide

important information of how well a certain drug is able to inhibit its direct target as well as other immune axes, and what is the relationship between inhibition of certain immune pathways/products and restoration of the barrier abnormalities characterizing AD, as well as clinical measures of the disease. Blood represents an easier accessible source of biomarkers, due to the relatively easy collection by blood withdrawal, in contrast to the invasive skin biopsy necessary for the assessment of biomarkers in the skin. In addition, blood levels may more objectively represent overall skin involvement, whereas skin biopsy represents only the skin where the biopsy is performed. Unfortunately, although skin biopsies accurately reflect disease severity and robust changes can be found early in the skin of patients with AD with various treatments, changes in blood may be more subtle and/or may take longer to occur.[20,158] In addition, some key AD biomarkers in skin (ie, CCL26/exotoxin-3)[84] are not well detected in blood, limiting the use of blood as a surrogate to skin biopsies. Biopsies collected from skin could be further divided into lesional and nonlesional samples. Perhaps counterintuitively, mRNA

TABLE V. GRADE evidence profile: Accumulated data on potential biomarkers correlating with disease severity in AD*

Biomarker No. of studies; No. of subjects included	Weighted average of correlation strength (*r*)*	Limitation	Inconsistency	Indirectness/ impreci-sion/publication bias	Overall evidence for biomarker generalizability (highest achieved)
Biomarkers correlating with severity in nontreated adult AD					
CCL17/TARC 14; 1,136	0.58	No serious limitations for blood; for skin—limited number of studies were found by our criteria	Not all studies correlated the biomarker with EASI or SCORAD as scores for AD clinical severity	No serious indirectness or imprecision; no publication bias detected	Very high (in blood)
IgE 11; 421	0.62	No serious limitations	No serious inconsistency among these reports, but IgE levels are not consistently correlated with AD severity in multiple other reports	No serious indirectness or imprecision; no publication bias detected	High
CCL22/MDC 9; 227	0.62	No serious limitations for blood; for skin—limited evidence exists by our criteria	No serious inconsistency	No serious indirectness or imprecision; no publication bias detected	High (in blood)
LDH 7; 445	0.52	No serious limitations	No serious inconsistency	No serious indirectness or imprecision; no publication bias detected	High
IL-18 5; 321	0.63	No serious limitations	Variable laboratory methods in skin	No serious indirectness or imprecision; no publication bias detected	High
Eosinophils/ ECP 9; 253	0.6	No serious limitations	Variable laboratory methods were reported. Different aspects of eosinophil upregulation/ activation were analyzed	No serious indirectness or imprecision; no publication bias detected	Moderate-high
IL-22 7; 116	0.52	Sparse reports in blood, with limited number of patients	Variable laboratory methods in blood	No serious indirectness or imprecision; no publication bias detected	Moderate (in skin)
IL-13 6; 144	0.54	Sparse data in blood by our criteria. Limited number of patients in both skin and blood studies	Variable laboratory methods in blood	No serious indirectness or imprecision; no publication bias detected	Moderate (in skin)
E-selectin 4; 159	0.53	No serious limitations	Laboratory and correlation methods and varied	No serious indirectness or imprecision; no publication bias detected	Moderate
MMP12 5; 174	0.46	No serious limitations for skin. Only proteomic data were reported in blood by our criteria	Laboratory and correlation methods and varied	No serious indirectness or imprecision; no publication bias detected	Moderate
S100A7/12 6; 132	0.49	No serious limitations	No serious inconsistency	No serious indirectness or imprecision; no publication bias detected	Moderate
CCL27/CTACK 2; 126	0.59	Limited evidence in blood, no evidence in skin by our criteria	Different AD severity scores were used	No serious indirectness or imprecision; no publication bias detected	Moderate-low (in blood)

(Continued)

TABLE V. *(Continued)*

Biomarker No. of studies; No. of subjects included	Weighted average of correlation strength (*r*)*	Limitation	Inconsistency	Indirectness/ imprecision/publication bias	Overall evidence for biomarker generalizability (highest achieved)
CCL26/eotaxin-3 3; 72	0.53	Very limited data in skin	No serious inconsistency	No serious indirectness or imprecision; no publication bias detected	Moderate-low (in blood)
CCL18/ PARC 2; 22	0.63	Very limited data in adult skin; no data from adult blood by our criteria	No serious inconsistency	No serious indirectness or imprecision; no publication bias detected	Low
IL-19 2; 136	0.59	No data were reported in adult skin by our criteria. The largest study in adult blood only achieved $P < .1$	No serious inconsistency	No serious indirectness or imprecision; no publication bias detected	Low (in blood)
Biomarkers correlating with severity in nontreated pediatric AD					
CCL17/TARC 9; 559	0.56	No serious limitations in blood. No data were reported in pediatric skin by our criteria	No serious inconsistency	No serious indirectness or imprecision; no publication bias detected	High (in blood)
CTACK/CCL27 4; 254	0.66	No serious limitations in blood. No data were reported in pediatric skin by our criteria	No serious inconsistency	No serious indirectness or imprecision; no publication bias detected	High (in blood)
IgE, 3; 118 IL-18, 4; 155, CCL22/MDC, 4; 131	0.76, 0.64, 0.46 (respectively)	Limited number of studies by our criteria. For CCL22/ MDC, correlation was found only in blood	No serious inconsistency	No serious indirectness or imprecision; no publication bias detected	Moderate-high (in blood)
E-selectin, 2; 45	0.45	Limited evidence in pediatric blood; no data from pediatric skin by our criteria	Variable laboratory methods	No serious indirectness or imprecision; no publication bias detected	Moderate-low (in blood)
Eosinophils/ ECP 3; 128	0.71	Limited number of studies by our criteria	Variable laboratory methods	No serious indirectness or imprecision; no publication bias detected	Moderate-low
CCL18/PARC 3; 148	0.47	Limited number of studies by our criteria	No serious inconsistency	No serious indirectness or imprecision; no publication bias detected	Moderate-low
IL-22, 1; 19 IL-13, 1; 21 S100A7/12, 1; 21	NA	Very limited number of studies and subjects in pediatric skin; no evidence in pediatric blood by our criteria	No serious inconsistency	No serious indirectness or imprecision; no publication bias detected	Low (in skin)
MMP12 2; 49	0.5	Very limited number of studies and subjects in both skin and blood by our criteria	In blood, correlation was found with body surface area. In skin, correlation was found with pruritus	No serious indirectness or imprecision; no publication bias detected	Low
IL-19 3; 59	0.43	Limited evidence in pediatric skin; no evidence in pediatric blood by our criteria. Tape-stripped pediatric skin only achieved $P < .1$	No serious inconsistency	No serious indirectness or imprecision; no publication bias detected	Low (in skin)

(Continued)

TABLE V. *(Continued)*

Biomarker No. of studies; No. of subjects included	Weighted average of correlation strength (*r*)*	Limitation	Inconsistency	Indirectness/ impreci-sion/publication bias	Overall evidence for biomarker generaliz-ability (highest achieved)
Biomarkers showing decreased levels in correlation with clinical improvement in longitudinal, topical treatment studies					
CCL17/TARC, CCL22/MDC, 1; 20 (for both)	NA	Limited data and only with an emollient. Correlation was found only in patients with moderate AD	No serious inconsistency	No serious indirectness or imprecision; no publication bias detected	Low†
S100A7/8/12 1; 40	NA	Limited data and only with crisaborole	Unlike other potential biomarkers, correlation was found with Investigator's Static Global Assessment and not EASI/SCORAD	No serious indirectness or imprecision; no publication bias detected	Low
Biomarkers showing decreased levels in correlation with clinical improvement in longitudinal, systemic treatment studies					
CCL17/TARC 6; 170	0.55	No serious limitations	During dupilumab treatment, biomarker reduction was correlated with pruritus	No serious indirectness or imprecision; no publication bias detected	Moderate-high (in blood)
CCL13/MCP-4, 5; 130, IL-13, 5; 159, CCL22/MDC, 4; 124	0.54, 0.56, 0.49 (respectively)	Sparse data in blood by our criteria	During dupilumab treatment, correlation with biomarker reduction only achieved *P* < .1. For CCL13/MCP-4, variable laboratory methods were reported	No serious indirectness or imprecision; no publication bias detected	Moderate-high (in skin)†
S100A7/8/12 4; 121	0.54	No serious limitations	No serious inconsistency	No serious indirectness or imprecision; no publication bias detected	Moderate
IL-22 4; 92	0.56	Limited evidence in skin; no evidence in blood	No serious inconsistency	No serious indirectness or imprecision; no publication bias detected	Moderate-low
CCL18/PARC 3; 98	0.56	Limited evidence in skin; sparse evidence in blood by our criteria	No serious inconsistency	No serious indirectness or imprecision; no publication bias detected	Moderate-low
CCL26/ eotaxin-3 3; 73	0.62	No evidence in blood by our criteria	No serious inconsistency	No serious indirectness or imprecision; no publication bias detected	Moderate-low (in skin)

EASI, Eczema Area and Severity Index; *ECP*, eosinophil cationic protein; *LDH*, lactate dehydrogenase; *NA*, not applicable because only 1 report was included by our criteria; *PARC*, pulmonary and activation-regulated chemokine; *SCORAD*, SCORing of Atopic Dermatitis.

*Based on Tables III and IV, only studies with a significant positive correlation with a correlation coefficient of ≥0.4 were included.

†Baseline CCL22/MDC expression in skin correlated with future clinical improvement in a report analyzing data across multiple studies (using both topical and systemic therapies) at various time points.[108]

expression levels of markers from nonlesional skin samples of untreated patients with AD show higher and more significant correlations with SCORing of Atopic Dermatitis, including general inflammatory (metalloproteinase 12 [MMP12])- and proliferation (keratin 16 [KRT16])-related markers, as well as markers related to T_H22 (IL-22), T_H17 (CXCL1), and T_H17/T_H22 (S100A9).[58] Moreover, nonlesional untreated skin data better correlate with serum data as compared with lesional skin, whereas correlations between lesional skin and serum are sparse.[43,58] A possible explanation is that lesional AD skin bears a highly inflamed background, making the AD-specific biomarkers harder to identify and dissect due to a dilution phenomenon of innate cytokines. Furthermore, because nonlesional AD skin is not normal and yet not as inflamed as lesional skin, it provides a unique window for assessing AD dissemination to apparently uninvolved skin, and interventions that normalize nonlesional skin have the hypothetic potential to also prevent AD development.

Nevertheless, although skin biopsies are feasible in proof-of-concept studies in which it is crucial to understand the mechanism of action, and are highly informative, biopsies may be associated

TABLE VI. Comparison of biomarker assessment by tape-strips and full-thickness skin biopsies

Parameter	Tape-strips	Skin biopsies
Detection rates	Limited sample detection rates of 50% or even less in some studies[23,154,159,160]	Typically, very high
Depth of tissue sampled	Stratum corneum and some of the stratum granulosum	Entire epidermis and dermis (when punch biopsies are used)
Detection of key T_H2/T_H22, AD-related biomarkers	Limited in some studies (eg, IL-4/IL-13 and IL-5,[23] IL-31[23,68,93,154,159,160,163])	Usually captured well
Detection of epidermal barrier-related biomarkers	Captured well (eg, terminal differentiation markers such as FLG and LOR, lipid-related biomarkers such as ELOVL1-7).[9,23,68,154,159,163] Expression of some biomarkers was correlated with biopsies in the same individuals.[164] A recent report suggested tape-stripped skin may even capture barrier-related changes better than biopsied skin in early disease[81]	Usually captured well. Barrier-related changes can be located at specific areas of the skin
Advantages	Minimally invasive, nonscarring, allows repeated testing even in pediatric patients	Provides enough tissue for various laboratory studies, including for full-thickness immunohistochemistry studies revealing structural changes
Disadvantages	Tissue processing is time-consuming and technically challenging; potential differences in depth of tape-stripped skin, location of biomarkers, and structural changes (eg, epidermal thickness) within the skin cannot be captured. Hyperlasia-related biomarkers (eg, K16 and Ki67) are not well captured	Painful, scarring (including hypertrophic/keloids), might be complicated by infections, poor healing

ELOVL, Elongation of very long chain fatty acids protein; *LOR,* loricrin.

with significant discomfort and complications, making it difficult to use them in the setting of large-scale clinical trials and longitudinal studies, as well as in pediatric studies. Furthermore, incorporating skin and blood biomarker testing into large clinical trials, longitudinal studies, and in the clinic may be challenging and, if it is to be adopted in the future, will require very simple testing methods.

Consequently, there is a large unmet need for development of minimally invasive cutaneous biomarkers that capture the AD profile of lesional and nonlesional skin. Recently, tape-strips studies, collecting stratum corneum proteins from both adults and children with AD, showed promise in defining key disease features.[68,106,159-161] These include studies of predefined sets of proteins and genes, as well as a limited-scope RNAseq.[68,106,159,160,162] Similar to mRNA data from skin biopsies, tape-strips from both lesional and nonlesional skin show significant correlations with disease severity.[68,93,159,160] Comparisons of variable aspects of tape-strips and biopsies are presented in Table VI, including disadvantages that may limit the use of tape-strips in settings of clinical trials or longitudinal studies. Recently, transcriptomic studies by tape-strip collection in young children and adults with AD showed improved detection rates of close to 100% per sample and per marker, perhaps enabling this approach in larger-scale studies, without losing data.[9,68] This may indicate that in the future it may be feasible to use tape-strips in larger clinical trials and longitudinal studies, and even in the clinic.

Conclusions

The accessibility of the skin makes it the perfect tissue for investigation of disease mechanisms, and bench-to-bedside translational approaches are rapidly facilitating the development of novel therapeutics for inflammatory skin diseases. Tissue-derived biomarkers may further accelerate clinical trials and allow better reproducibility and rigor.[165] Nevertheless, the discovery of a

novel, validated disease-related biomarker is demanding and requires multiple steps, from the first detection of the potential tissue-derived factor to the final confirmation and acceptance by regulatory organizations.

AD, a common yet complex skin disease, stemming from immune dysregulations as well as epidermal barrier abnormalities, still poses a therapeutic challenge. The "one-size-fits-all" approach does not always apply for AD, because diverse disease phenotypes have been recognized, and therapeutic response may vary on the basis of their clinical and molecular differences. Indeed, a survey of AD specialists (IEC councilors and associates) strongly supports the combination of clinical evaluation with biomarkers' assessments for stratification of patients with AD due to the large heterogeneity of the disease. Despite the relatively easy inspection of the skin by physical examination, clinical observations may not fully appreciate skin abnormalities, and are not entirely objective. This is emphasized by the relatively normal clinical appearance of AD nonlesional skin, while tissue assessments unearth significant immune and barrier dysregulations, resembling lesional skin.[42,166] As we move toward more targeted therapies, AD biomarkers are important to appreciate patient-specific molecular dysregulations that differ between various AD subtypes. Because biologics are expensive, characterization of biomarkers that predict which patients will likely benefit most from these targeted biologics is essential. Ideally, a validated set of reliable biomarkers using minimally invasive methods will allow the implementation of precision medicine in AD, improve patient management, and expedite the development of novel therapeutics.

Because a biomarker should be assessed repeatedly, especially in the context of treatment monitoring or longitudinal studies, the preference of less-invasive methods over skin biopsies is well understood. Furthermore, skin biopsies are even harder to obtain in the pediatric population, in which the burden of AD is most significant. It is thus not surprising that alternative methods for skin sampling are emerging, with tape-strips, a minimally
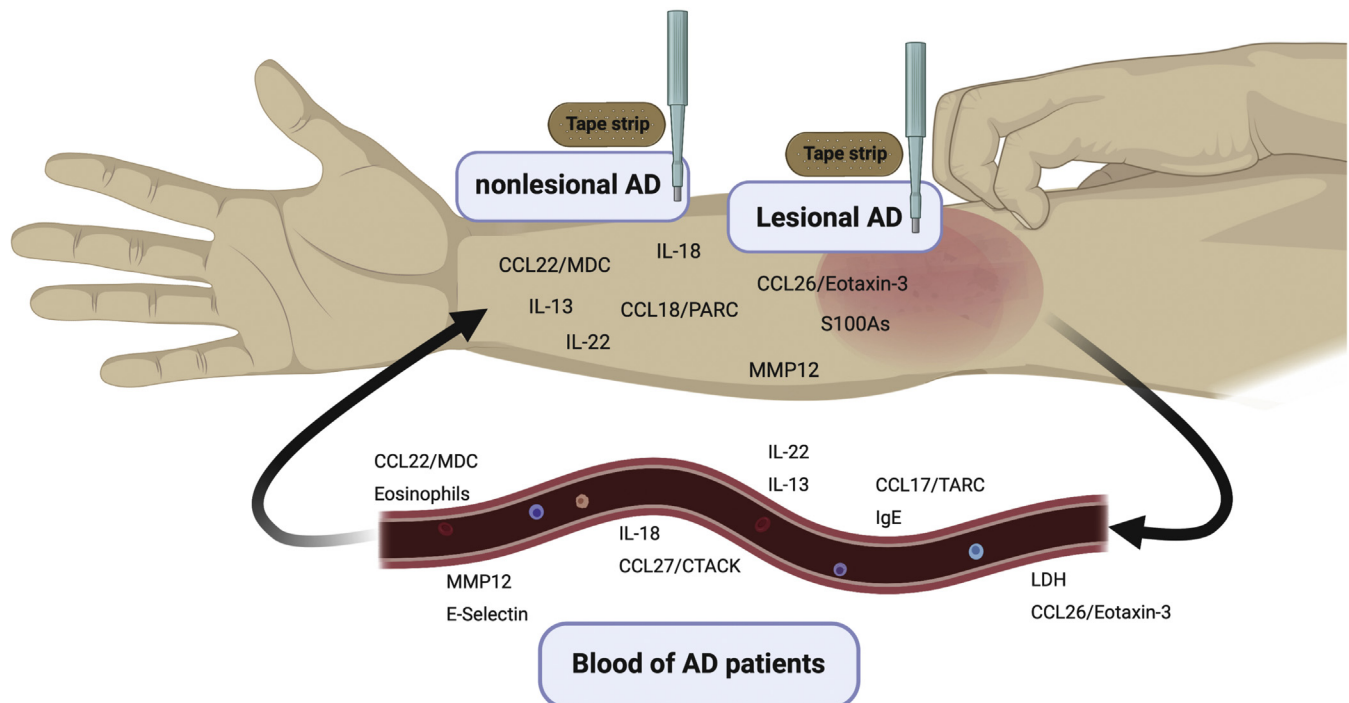
FIG 1. Potential biomarkers for AD in nonlesional and lesional AD skin (using both biopsies and tape-strips, *top*) as well as circulating potential biomarkers in blood of patients with AD (*bottom*). *LDH*, Lactate dehydrogenase.

invasive method sampling only superficial epidermal layers, showing promise in both adult and pediatric AD.[9,68,81,154,159,160]

A biomarker should be biologically relevant and linked to disease mechanism.[165] AD is characterized by robust systemic and cutaneous immune activation,[167] with a dominant T_H2-skewing that is shared across AD subtypes.[168] Currently, some clinicians are already assessing few potential AD-related blood biomarkers to complement the physical examination and assess severity more accurately. These include nonspecific markers of inflammation and atopy. Nevertheless, the chemokine with the greatest evidence-based support to become a potential AD biomarker, at both baseline and following therapy, is CCL17/TARC, a chemoattractant of T_H2 cells. Although CCL17/TARC is implicated in other atopic diseases as well, including asthma and allergic rhinitis,[169,170] correlation with clinical severity was established only in patients with AD.[27] Moreover, we were able to find more than 20 publications supporting the robust correlation of serum CCL17/TARC with AD clinical severity, mainly SCORing of Atopic Dermatitis, in both children and adults. Additional emerging potential biomarkers include other T_H2-related chemokines, such as CCL18/pulmonary and activation-regulated chemokine, CCL22/MDC (recently reported to consistently predict therapeutic response across different treatments),[137] CCL26/eotaxin-3, CCL27/CTACK, and the key T_H2 and T_H22 cytokines, that is, IL-13 and IL-22, respectively. In comparison to T_H2-related chemokines, cytokines were less commonly reported as blood biomarkers for AD and were mostly found to correlate with severity when assessed in skin.

In conclusion, the potential of biomarkers in AD is yet to be fully elucidated. The significant burden of the disease, its heterogeneity with increasingly recognized various subtypes, and the challenges of developing a "magic bullet" that benefits all patients despite the progression of multiple novel therapies advocate for a precision medicine approach. This approach would benefit from a set of disease-specific biomarkers that will further facilitate AD research and improve patient management; however, as demonstrated by our GRADE-based evaluation, evidence on biomarkers is still lacking.

New studies using more minimal techniques such as tape-strips, including pretreatment and posttreatment assessments, in which biomarker dynamics are closely monitored in relation to therapeutic response, are needed to improve the validity and relevance of biomarkers in AD. Large-scale clinical trials with extensive biomarker evaluation, including patients with variable AD phenotypes (eg, variable races and ages), are critical to establish the potential role of biomarkers in AD management. These may lead in the future to a clinical approach using biomarkers as a practical clinical tool where AD treatment will be personally tailored.

The figure was created with BioRender.com.

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IEC SURVEY ON BIOMARKERS IN AD

- Are you using blood tests/biomarkers for the diagnosis of AD?
  - o No
  - o Yes
- Which are you using?
  - o IgE
  - o Eosinophils
  - o Other (please specify)
- Do you think that blood tests/biomarkers are useful for assessing the severity of AD?
  - o No
  - o Yes
- If no, why?
- If yes, why?
  - o Improve selection of patients for therapy or trials improve the comparability of trials
  - o For follow-up in daily practice
  - o Other (please specify)
- Which would you suggest?
  - o CCL17
  - o LDH
  - o Eosinophils
  - o IgE
  - o CCL22
  - o CCL26
  - o sIL-2R (soluble IL-2 receptor)
  - o IL-22/IL-13/p-EASI (CCL17/IL-22/sIL-2R)
  - o Other (please specify)
- Could blood test/biomarkers be useful for assessing treatment compliance?
  - o No
  - o Yes
- How?
- Which biomarkers would you suggest?
- Do you think that AD is a heterogeneous disease?
  - o No
  - o Yes
- How many different subtypes/phenotypes of AD do you think are existing?
  - o 1
  - o 2
  - o 3
  - o >3
- How would you proceed to stratify the heterogeneous phenotype?
  - o Only by clinical features
  - o Only by biomarkers
  - o Combining clinical features and biomarkers
- What clinical features would you suggest?
- Which biomarkers would you suggest?
  - o Genetics
  - o Genomics/transcriptomics in skin biopsies
  - o Soluble markers/proteomics in blood samples
  - o Tape-strip proteomic analyses
  - o Tape-strip genomic/transcriptomic analyses
  - o TEWL
  - o Other biomarker analyses
- Which soluble markers/proteomics would you suggest?
  - o IgE
  - o LDH
  - o Eosinophils
  - o TARC/CCL17
  - o Other (please specify)
- Which clinical features would you suggest?
- Which groups of biomarkers would you suggest?
  - o Genomics/transcriptomics in skin
  - o Genomics/transcriptomics in tape-strips
  - o Soluble markers/proteomics in skin
  - o Soluble markers in blood
  - o Proteomics in tape-strips
  - o Physiological properties (eg, TEWL and Raman)
  - o Other (please specify)
- Which soluble markers/proteomics would you suggest?
  - o IgE
  - o LDH
  - o Eosinophils
  - o Other (please specify)
- How would you prioritize the needs for blood test/biomarkers? (1 is the highest priority and 10 is the lowest)

Better biomarkers for diseases severity	1	2	3	4	5	6	7	8	9	10
Better diagnostic biomarkers (eg, in adult-onset AD)	1	2	3	4	5	6	7	8	9	10
Less-invasive biomarkers (eg, skin strips) for use in infants (or "field studies")	1	2	3	4	5	6	7	8	9	10
Better biomarkers for prediction of treatment response	1	2	3	4	5	6	7	8	9	10
Better biomarkers as readout of treatment response (eg, to enable comparison of the effectiveness of different treatments)	1	2	3	4	5	6	7	8	9	10
Better biomarkers for identification of endo(pheno) types to predict treatment response to systemic treatment/biologics	1	2	3	4	5	6	7	8	9	10
Biomarkers that will be able to identify responders to a particular drug before initiation of treatment	1	2	3	4	5	6	7	8	9	10
Biomarkers that will stratify responders and nonresponders in clinical trials	1	2	3	4	5	6	7	8	9	10
Biomarkers to predict the natural course of the disease (eg, in infants)	1	2	3	4	5	6	7	8	9	10
Biomarkers to predict the disease development/determine persons at risk to develop AD (in infants)	1	2	3	4	5	6	7	8	9	10

EASI, Eczema Area and Severity Index; *LDH*, lactate dehydrogenase; *TEWL*, transepidermal water loss.