


ORIGINAL ARTICLE

Requirements and expectations of high-quality biomarkers for atopic dermatitis and psoriasis in 2021—a two-round Delphi survey among international experts

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Abstract

Background Chronic inflammatory skin diseases such as atopic dermatitis (AD) and psoriasis (PSO) present major challenges in health care. Thus, biomarkers to identify disease trajectories and response to treatments to improve the lives of affected individuals warrant great research consideration. The requirements that these biomarkers must fulfil for use as practical clinical tools have not yet been adequately investigated.

Aim To identify the core elements of high-quality AD and PSO biomarkers to prepare recommendations for current biomarker research.

Method A cross-sectional two-round Delphi survey was conducted from August to October 2019 and October to November 2020. All participants were members of the BIOMAP project, an EU-funded consortium of clinicians, researchers, patient organizations and pharmaceutical industry partners. The first round consisted of three open-ended questions. Responses were qualitatively analysed, and 26 closed statements were developed. For the second round, 'agreement' was assumed when the responses of $\geq 70\%$ of the participants were ≥ 5 points on a 7-point Likert scale for each statement. Priority classification was based on mean scores (<20th percentile = low, 20th to 60th percentile = medium, >60th percentile = high).

Results Twenty-one and twenty-six individuals participated in rounds one and two, respectively. From 26 statements that were included in round 2, 18 achieved agreement (8 concerning the performance, 8 for the purpose and 2 on current obstacles). Seven statements were classified as high priority, e.g. those concerning reliability, clinical validity, a high positive predictive value, prediction of the therapeutic response and disease progression. Another seven statements were assigned medium priority, e.g. those about analytical validity, prediction of comorbidities and therapeutic algorithm. Low priority included four statements, like those concerning cost effectiveness and prediction of disease flares.

Conclusion The core requirements that experts agreed on being essential for high-quality AD and PSO biomarkers require rapid validation. Biomarkers can therefore be assessed based on these prioritized requirements.

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Conflicts of interest

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Introduction

Atopic dermatitis (AD) and psoriasis (PSO) are both common chronic inflammatory skin diseases that affect people of all ages globally.^{1,2} The prevalence of AD is estimated to be around 20% in the paediatric population and up to 10% in adults in high-income countries, with recent studies suggesting that adult AD is more common than previously thought.^{3–6} Occurring more frequently with advancing age, the reported prevalence of PSO ranges between 0% and 1.4% in children and up to 11.4% in adults.⁷ Both diseases are highly variable in terms of disease onset, severity, progression over time and treatment response.^{5,7} In addition, both conditions are accompanied by significant

morbidity and an increased risk for associated conditions such as arthritis and asthma.^{6,7}

The entire dermatological field is currently experiencing substantial developments, and the current disease classification based on antiquated nomenclature is being rebuilt based on an improved understanding of the underlying pathophysiology.^{8,9} Nevertheless, the immunopathogenesis of both AD and PSO is not fully understood, and both diseases represent a complex combination of genetic, environmental and immunological factors.^{10,11} Although multiple FDA- and EMA-approved targeted therapies are available already,¹² there is significant interpatient heterogeneity in efficacy and tolerability, and not all patients benefit equally.^{1,13–15} A major reason for suboptimal treatment response is that conventional treatment methods often require a timely and precise diagnosis, which is often not possible in all cases. Furthermore, the response to certain therapies cannot be

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reliably predicted. Thus, these skin conditions still have a wide-ranging impact on quality of life, including social, economic and professional aspects of a patient's life. The immense direct and indirect costs for affected individuals, their families and healthcare systems highlight the need for optimal person-centered care.^{1,13–16}

Biomarkers are generally defined as 'any substance, structure or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease'.¹⁷ Biomarkers can therefore aid in identifying AD and PSO and can play a role in improving patient care by predicting disease trajectories and responses to specific treatments.¹⁸ However, the identification, validation and transfer of a biomarker into clinical practice is complex and time-consuming, and despite many efforts for AD and PSO, no biomarker has yet been transferred into routine clinical practice.^{18–20} To advance this process, the European research project entitled BIOMAP (Biomarkers in Atopic Dermatitis and Psoriasis)²¹ from the Innovative Medicines Initiative (IMI) was established in 2019 with the aim to improve the understanding of disease subtypes, mechanisms and outcomes, and to discover potential biomarkers. In this project, one of the essential first steps was to specify which requirements high-quality biomarkers must fulfil. There are already general and disease-specific recommendations regarding requirements for suitable biomarkers and biomarker studies.^{22–25} However, none of those are specific to AD and PSO.

Therefore, this study aimed to obtain consensus from the international experts from the BIOMAP consortium regarding the core elements of high-quality AD and PSO biomarkers to prepare medical recommendations. Additionally, it aimed to identify research priorities to overcome obstacles in the use of AD and PSO biomarkers.

Methods

Study design

A cross-sectional two-round survey was conducted in accordance with the Delphi method from August to October 2019 and again from October to November 2020. The Delphi technique is an iterative multistage process, designed to transform opinions into group consensus, that is used commonly within health sciences.²⁶ The classic method involves sending an open-ended set of questions to the participants and analysing their response. This is then used to develop a new questionnaire and the circle is repeated.²⁷ There exist no set guidelines for deciding on the optimum number of participants because this depends on the purpose of the survey. While the classic Delphi method involves 4 rounds, the modified technique is limited to 2 rounds to minimize loss of acceptable response rates because of the prolonged duration of the overall process and its negative influence on panellists' interest.²⁷ In the present study, the modified Delphi method was used.

The members of BIOMAP were chosen because of their extensive knowledge, expertise and ability to make comprehensive and meaningful contributions to the subject.

Recruitment and data collection

In rounds one and two, 108 members of BIOMAP were sent an e-mail invitation with a link to the online survey. Included were (1) brief participation information outlining the study's aim, (2) the definition of a biomarker using the definition from FDA-NIH (Food and Drug Administration (US); National Institute of Health (US) working group's 'Biomarkers, EndpointS and other Tools' resource (BEST)),²⁸ (3) demographic questions and (4) the survey questions. Demographic data were collected at the end of each round. A reminder e-mail was sent 2 weeks following the initial invitation. Nonparticipation in round one did not exclude participation in round two.

Round one aimed to collect a broad range of opinions using three open-ended questions in accordance with the classic Delphi approach.²⁷ The survey was pretested by three BIOMAP members who were not involved in the study development. The survey was amended based on their feedback. The three pretesters were excluded from actual Delphi participation.

Participants were asked to provide their expert opinion on: (1) what requirements a biomarker needed to fulfil to be useful for AD and/or PSO, (2) what clinically meaningful outcomes a biomarker should deliver for patients with AD and/or PSO and (3) what main obstacles needed to be overcome before biomarkers could be implemented into daily clinical use for patients with AD and/or PSO. Participants could either provide a general answer or differentiate between diagnostic, monitoring, predictive, prognostic and safety biomarkers.

Answers from the first round were used to develop a list of statements for the second round that encompassed 26 statements classified into 3 sections: (1) the biomarker 'performance' (8 statements, e.g. on reliability, clinical validity), (2) the 'purpose' of the biomarker (9 statements, e.g. on therapeutic response, adherence) and (3) relevance of potential obstacles preventing widespread use (9 statements, e.g. on technical requirements, unfamiliarity). Participants were asked to rate each statement on a 7-point Likert scale from 1 (strongly disagree) to 7 (strongly agree) with a neutral mid-point (4, neither disagree nor agree). Participants were also asked to provide comments on missing criteria in the respective categories. Additionally, participants were asked to choose up to three research priorities that should be focused on to reduce obstacles. Based on information from round one, the answers 'more validation studies', 'focus on becoming less invasive', 'simplify technical procedures', 'increase popularity and knowledge', 'improve reimbursement', 'ensure timely information', 'define gold-standard diagnostics' and 'harmonize and create data sources' were available to choose.

Statistical analysis

Only completed questionnaires were considered. Demographic data including country, interest in AD and/or PSO and main area of expertise (patient, patient support organization, pharmaceutical company, physician or research scientist) were collected from each round and input into SPSS, Version 26 (IBM Corporation, Armonk, NY, USA). Data analysts were blinded to participants' identities.

Open-ended responses from round one were compiled from the online survey tool into Microsoft Excel and analysed using a deductive-inductive content-analysis approach by C.S. and K.E., providing guidance and oversight of codes and categories. Any uncertainties were discussed until an agreement was met. Answers were modified or excluded based on the following reasons: (1) irrelevance for the topic/study, (2) misunderstandings of the question, (3) repetitions in meaning or intent or (4) information already encompassed in another comment. The remaining comments were processed for the questionnaire in round two.

In round two, descriptive data for each item were obtained, including the mean Likert score, standard deviation (SD) and median. A target 70% agreement for the score of 5 or more on the 7-point Likert scale for each statement was chosen *a priori*.²⁹ Based on this, statements were considered for inclusion in the biomarker recommendations. Subsequently, statements that reached consensus were ranked according to their mean score as either 'low priority', 'medium priority' or 'high priority'. Taking into account that only statements of high importance are still included, only the lower 20% of means were ranked as low, middle 40% as medium and the remaining upper 40% as high priority. Statements from the section 'performance' and the section 'purpose' were collated into the AD and PSO biomarker recommendations. Statements from section category 'obstacles' were intended to function as a supplement for further research. Open-ended answers were screened for a possible extension of the recommendations.

Results

Characteristics

Of the 108 BIOMAP members, 21 (19.4%) completed the first Delphi round and 26 (24.1%) the second round, with a total of 35 members completing 1 round and 12 members completing both rounds. Of the 35 participants, the majority were research scientists ($n = 26$; 45.6%) followed by physicians ($n = 17$; 29.8%; [Table 1]). Additionally, participants were mainly interested/experienced in AD only ($n = 16$, 45.7%), while 12 participants (34.3%) were interested in both AD and PSO and seven (20.0%) in PSO only. Participants were from ten countries (United Kingdom, Germany, Netherlands, United States of America, Denmark, Switzerland, Austria, Estonia, Sweden and Australia).

Table 1 Demographics of Delphi participants

	n (%)		
	Total (n = 35)	Round 1 (n = 21)	Round 2 (n = 26)
Area of expertise*			
Research scientist	26 (74.2)	13 (61.9)	16 (61.5)
Physician**	17 (48.6)	9 (42.9)	12 (80.8)
Pharmaceutical industry	8 (22.9)	5 (23.8)	6 (23.1)
Patient support organization	4 (11.4)	0 (0)	4 (15.4)
Patient	2 (0.6)	2 (9.5)***	2 (7.7)***
Country			
United Kingdom	12 (34.3)	8 (38.1)	9 (34.6)
Germany	5 (14.3)	3 (14.3)	4 (15.4)
Netherlands	5 (14.3)	2 (9.5)	4 (15.4)
United States	4 (11.4)	2 (9.5)	3 (11.5)
Denmark	3 (8.6)	2 (9.5)	2 (7.7)
Switzerland	2 (5.7)	1 (4.8)	1 (3.8)
Austria	2 (5.7)	1 (4.8)	1 (3.8)
Estonia	1 (2.9)	0 (0)	1 (3.8)
Sweden	1 (2.9)	1 (4.8)	0 (0)
Australia	1 (2.9)	1 (4.8)	1 (3.8)
Interest			
AD	16 (45.7)	10 (47.6)	10 (38.5)
AD and PSO	12 (34.3)	6 (28.6)	9 (34.6)
PSO	7 (20)	5 (23.8)	7 (26.9)

*Participants could choose more than one area of expertise (i.e. cumulative percentages >100%).

**Physician's discipline was not further specified.

***One patient indicated his/her interest in AD, the other one in PSO.

AD, atopic dermatitis; PSO, psoriasis.

General results

The 3 open-ended questions from round 1 were grouped, reduced and collated into 26 statements for round 2 (Fig. 1). In round 2, 18 statements (65.4%) reached consensus for inclusion in the PSO and AD biomarker recommendations. As shown in Table 2, the percentages of consensus ranged from 73% to 100%, with the 'cost-effectiveness' statement having the lowest percentage and the 'reliability' and 'clinical validity' statements having the highest. Mean ratings ranged from 4.04 to 6.42, with the highest mean rating for 'therapeutic response' (mean = 6.42, SD = 0.86).

Performance

Agreement was reached for all eight items (range: 73–100%). The highest percentages were reached for statements claiming that biomarkers for AD and PSO should have a high-test reliability and a high clinical validity. Mean scores ranged from 5.12 (SD = 1.21) to 6.35 (SD = 0.69), indicating 4 high-priority recommendations, 3 medium priority recommendations and 1 low-priority recommendation (Table 2).

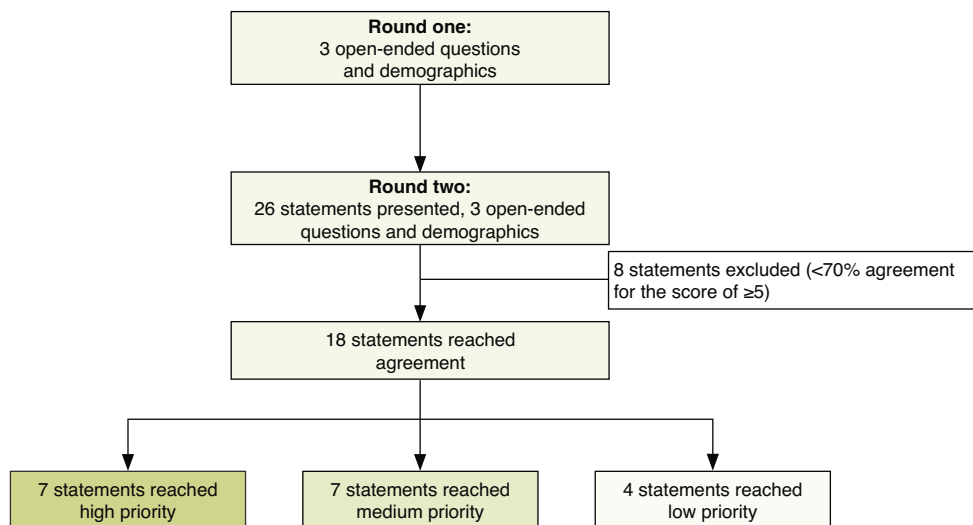


Figure 1 Flow chart illustrating the two-stage Delphi process. Statements were categorized according to their mean score (0.20—percentile = low priority, 0.60—percentile = medium priority; >0.6—percentile = high priority).

Purpose

For statements indicating that biomarkers should reflect adherence to therapy, there was only 33.5% agreement (mean = 4.04, SD = 1.28). Consensus was reached for the other eight statements (73.1–96.1%), with the highest percentage for the therapeutic response statement. Two statements were categorized as high priority, four as medium priority and two as low-priority recommendations (Table 2).

Obstacles

Of the 9 statements, 7 had discrepancies in agreement, with agreement ranging between 46.1% and 65.4% and a mean score ranging from 4.12 to 4.92. The only two statements that achieved agreement in this category were ‘biomarkers are not validated by independent research/studies’ (92.4%; mean = 5.92, SD = 1.20) and ‘data sources needed to identify biomarkers are missing’ (73.1%; mean = 5.19, SD = 1.63).

Nearly all participants ($n = 24$, 92.3%) indicated that more validation studies should be performed, and half of all participants ($n = 13$, 50.0%) stated that harmonization, the creation of a data source ($n = 13$; 50%) and the definition of gold-standard diagnostics ($n = 12$; 46.2%) are of priority. The final list of recommendations is presented in Table 3.

Discussion

This study presents the first AD- and PSO-specific recommendations for high-quality AD and PSO biomarkers collated by an international panel of experts from the BIOMAP consortium. Consensus was achieved for 18 statements, while 8 statements

had discrepancies in agreement (less 70% agreement), predominately for the section ‘obstacles’. Of the highest importance were the performance elements reliability, clinical validity, relevance and high positive predictive value. A biomarker’s most important purpose was considered the prediction of therapeutic response and disease progression. Insufficient validation by independent researchers was identified as a major obstacle to the transfer of AD and PSO biomarkers in clinical practice. Validation and further studies were considered a high-priority research objective by all experts.

The rejection of most statements in the section ‘obstacles’ might be explained by the fact that the provision of sufficient patient data (e.g. molecular data) for biomarker identification, and good validation of biomarkers is paramount at this stage of biomarker processes. The need for sufficient data and independent studies has already been determined by previous studies.^{18,19,30} These data and studies are of particular importance to ensure quality criteria such as reliability and clinical utility. The establishment of nationwide disease registries, national cohorts^{31,32} and local birth cohorts,³³ and the promotion of international networks such as BIOMAP²¹ can contribute to sufficient data needed for the essential requirements for high-quality biomarkers. Moreover, the harmonization of data driven by the BIOMAP glossary³⁴ may facilitate cross-cohort analyses and increase the potential to identify small-effect estimates and stratification of disease subtypes.³⁵

Barriers, like low awareness, lack of cost-effectiveness and inadequate reimbursement, technical requirements and delayed test results, may become more relevant in later stages of research as seen with well-established biomarkers for several cancer

Table 2 Summary of ratings for all statements that AD and psoriasis biomarkers should fulfil after Delphi round two (*n* = 26)

Statement	Strongly agree	Agree	Somewhat agree	Neither nor	Somewhat disagree	Disagree	Strongly disagree	Mean (SD) Median	Total % consensus Priority
Performance									
Reliability: Biomarkers should give the same result in the same sample independent of external circumstances	12 (46.2)	11 (42.3)	3 (11.5)	0 (0)	0 (0)	0 (0)	0 (0)	6.35 (0.69) 6	100 High priority
Analytical validity: Biomarkers should precisely measure what it is meant to measure	9 (34.6)	9 (34.6)	5 (19.2)	1 (3.8)	1 (3.8)	1 (3.8)	0 (0)	5.81 (1.28) 6	88.6 Medium priority
Clinical validity: Biomarkers should predict the clinically relevant outcome well	14 (53.8)	8 (30.8)	2 (7.7)	0 (0)	2 (7.7)	0 (0)	0 (0)	6.23 (1.16) 6.5	92.3 High priority
Positive predictive value: Biomarkers should have a high probability for the occurrence of the outcome of interest, given a positive prediction	7 (26.9)	11 (42.3)	8 (30.8)	0 (0)	0 (0)	0 (0)	0 (0)	5.96 (0.77) 6	100 High priority
Negative predictive value: Biomarkers should have a high probability of the absence of the outcome of interest, given a negative prediction	3 (11.5)	12 (46.2)	7 (26.9)	1 (3.8)	2 (7.7)	1 (3.8)	0 (0)	5.38 (1.23) 6	80.8 Medium priority
Relevance: Biomarkers should answer relevant questions about diagnosis, treatment, management or prevention of the disease depending on the biomarker purpose	12 (46.2)	7 (26.9)	5 (19.2)	1 (3.8)	0 (0)	1 (3.8)	0 (0)	6.04 (1.22) 6	92.3 High priority
Feasibility: Biomarker assessment should be feasible in terms of minimally invasive, easy to perform and not too time-consuming	6 (23.1)	10 (38.5)	6 (23.1)	3 (11.5)	0 (0)	1 (3.8)	0 (0)	5.62 (1.20) 6	84.7 Medium priority
Cost effectiveness: Biomarkers should reduce total healthcare costs even through testing come with associated costs (needs to set against the increased patient quality of life and reduced demand on health service)	3 (11.5)	7 (26.9)	9 (34.6)	5 (19.2)	1 (3.8)	1 (3.8)	0 (0)	5.12 (1.21) 5	73 Low priority
Purpose									
Diagnostic: Biomarkers should accurately reflect diagnosis, e.g. differentiated AD from PSO or other inflammatory diseases, indicated an endotype of AD/PSO	8 (30.8)	9 (34.6)	4 (15.4)	3 (11.5)	1 (3.8)	1 (3.8)	0 (0)	5.65 (1.36) 6	80.8 Medium priority
Severity: Biomarkers should reflect objective parameters e.g. SCORAD, EASI or PASI	3 (11.5)	9 (34.6)	8 (30.8)	4 (15.4)	0 (0)	4 (15.4)	0 (0)	5.19 (1.30) 5	76.9 Low priority
Flares: Biomarkers should predict disease flares prior to occurrence of clinical symptoms	2 (7.7)	7 (26.9)	12 (46.2)	4 (15.4)	0 (0)	0 (0)	1 (3.8)	5.12 (1.18) 5	80.8 Low priority
Prognostic: Biomarkers should predict disease progression, e.g. whether a disease is self-limited or becomes chronic	7 (26.9)	11 (42.3)	6 (23.1)	2 (7.7)	0 (0)	0 (0)	0 (0)	5.88 (0.91) 6	92.3 High priority
Comorbidities: Biomarkers should predict the risk to develop, e.g. allergic asthma in AD, psoriatic arthritis in psoriasis	5 (19.2)	11 (42.3)	8 (30.8)	1 (3.8)	0 (0)	1 (3.8)	0 (0)	5.56 (1.09) 6	92.3 Medium priority
Response: Biomarkers should predict therapeutic response to a given therapy for efficacy maximization	16 (61.5)	6 (23.1)	3 (11.5)	1 (3.8)	0 (0)	0 (0)	0 (0)	6.42 (0.86) 7	96.1 High priority
Safety: Biomarkers should predict the risk to develop side-effects to a given therapy for toxicity minimization	6 (23.1)	8 (30.8)	6 (23.1)	5 (19.2)	1 (3.8)	0 (0)	0 (0)	5.50 (1.18) 6	77 Medium priority
Therapeutic algorithm: Biomarkers should define, e.g. sequential treatment options in an individual	4 (15.4)	10 (38.5)	5 (19.2)	6 (23.1)	1 (3.8)	0 (0)	0 (0)	5.35 (1.18) 6	73.1 Medium priority

Table 2 Continued

Statement	Strongly agree	Agree	Somewhat agree	Neither nor	Somewhat disagree	Disagree	Strongly disagree	Mean (SD) Median	Total % consensus	Priority
Adherence/compliance: Biomarkers should reflect the extent to which the patient is taking therapy as prescribed	0 (0)	2 (7.7)	8 (30.8)	10 (38.5)	3 (11.5)	1 (3.8)	2 (7.7)	4.04 (1.28) 4	33.5	
Obstacle	n (%)									
Independent validation: Biomarkers are not validated by independent researchers/studies	10 (38.5)	8 (30.8)	6 (23.1)	1 (3.8)	0 (0)	1 (3.8)	0 (0)	5.92 (1.20) 6	92.4	High priority
Significance: Biomarkers indicate events that are too rare and not of common interest	1 (3.8)	10 (38.5)	6 (23.1)	5 (19.2)	3 (11.5)	1 (3.8)	0 (0)	4.92 (1.26) 5	65.4	
Invasive assessment: Biomarker detection procedures are invasive	2 (7.7)	4 (15.4)	6 (23.1)	5 (19.2)	5 (19.2)	3 (11.5)	1 (3.8)	4.23 (1.61) 4	46.2	
Technical requirements: Biomarker detection requires high technical requirements	2 (7.7)	5 (19.2)	7 (26.9)	5 (19.2)	4 (15.4)	2 (7.7)	1 (3.8)	4.46 (1.56) 5	53.8	
Education and knowledge: Biomarkers are not commonly known (shareholders are unaware of their existence)	3 (11.5)	2 (7.7)	7 (26.9)	3 (11.5)	5 (19.2)	6 (23.1)	0 (0)	4.12 (1.68) 4	46.1	
Reimbursement: Biomarker determination is not reimbursed by stakeholders	3 (11.5)	1 (3.8)	8 (30.8)	9 (34.6)	1 (3.8)	4 (15.4)	0 (0)	4.36 (1.44) 4	46.1	
Time: Biomarker detection. It takes too long to get a result to provide clinical utility	1 (3.8)	4 (15.4)	7 (26.9)	5 (19.2)	5 (19.2)	2 (7.7)	1 (3.8)	4.15 (1.52) 4	46.1	
Performance evaluation: Gold-standard diagnostics are missing	3 (11.5)	6 (23.1)	4 (15.4)	7 (26.9)	4 (15.4)	0 (0)	2 (7.7)	4.58 (1.65) 4	50	
Biomarker identification: Harmonized large data sources are lacking to identify biomarkers	4 (15.4)	12 (46.2)	3 (11.5)	4 (15.4)	0 (0)	2 (7.7)	1 (3.8)	5.19 (1.63) 6	73.1	Low priority

AD, atopic dermatitis; EASI, Eczema Area and Severity Index; PASI, Psoriasis Area and Severity Index; SCORAD, SCORing Atopic Dermatitis.

Table 3 Checklist for future biomarkers based on the international Delphi expert consensus for atopic dermatitis and psoriasis

Statement	Explanation/Example based on the first survey round	Agreement Mean (SD) Median	Reached
Performance			
Reliability	Giving the same result in the same sample independent of external circumstances, e.g. different laboratories, time To be a reliable indicator for the presence of eczema in babies and young children	100% 6.35 (0.69) 6	
Clinical validity	Should predict the clinically important outcome well Correct interpretation of the biomarker measurement for the specific AD/psoriasis outcome includes a reduction in not just physical severity, but itch, mood (e.g. anxiety, low mood, depression and anger), fatigue	92.3% 6.23 (1.16) 6.5	
Relevance	Should provide some sort of benefit to AD and psoriasis patients Significant clinical utility can point to endotypes and subendotypes of the heterogeneous disease	92.3% 6.04 (1.22) 6	
Positive predictive value	Should have a high probability for the subject with a positive test to have the outcome of interest Sufficient sensitivity/specificity/predictive value dependent on the biomarker purpose	100% 5.96 (0.77) 6	
Analytical validity	Should precisely measure what it is meant to measure Accurate and precise measurement of the biomarker	88.6% 5.81 (1.28) 6	
Feasibility	Minimally invasive, easy to perform, not too time-consuming Feasibility of testing (time, easy in use)	84.7% 5.62 (1.20) 6	
Negative predictive value	Should have a high probability for the subject with a negative test not to have the outcome of interest Sufficient sensitivity/specificity/predictive value dependent on the biomarker purpose	80.8% 5.38 (1.23) 6	
Cost effectiveness	Is the biomarker cost-effective and with the aim of improved patient outcomes, and will it reduce healthcare costs	73% 5.12 (1.21) 5	
Purpose			
Therapeutic response	Response to a given therapy, e.g. ciclosporin, biologics for efficacy maximization Predict long-term response, response to therapy (clinical signs, symptoms and quality of life)	96.1% 6.42 (0.86) 7	
Disease progression	For example, a disease is self-limited or becomes chronic Phenotypic stratifier required, e.g. development of manifestations in eczema	92.3% 5.88 (0.91) 6	
Comorbidities	For example, allergic asthma in AD, psoriasis arthritis in psoriasis How likely is a person to also develop psoriasis arthritis, for example	92.3% 5.56 (1.09) 6	
Diagnosis accuracy	For example, differentiates eczema from psoriasis or other inflammatory skin diseases, indicate an endotype of eczema/psoriasis Definitive diagnosis of eczema in babies and children before symptoms present to enable parents to prepare and learn to manage.	80.8% 5.65 (1.36) 6	
Safety	For example, kidney problems with ciclosporin, conjunctivitis with dupilumab, candidiasis with iL-17 inhibitors Identify which treatment would have the greatest chance of being effective with the least side-effects	77% 5.50 (1.18) 6	
Therapeutic algorithm	For example, sequential treatment options in an individual person Those that predict best intervention at individual patient level i.e. understanding the best therapeutic intervention for an individual. Providing explanation for patients nonresponsive to certain therapies and offering alternative targeted therapy based on the biomarker profile	73.1% 5.35 (1.18) 6	
Severity	For example, an objective parameter reflecting scores such as SCORAD, EASI or PASI Detect or confirm presence and severity of AD or psoriasis and correlate with disease severity	76.9% 5.19 (1.30) 5	

Table 3 Continued

Statement	Explanation/Example based on the first survey round	Agreement Mean (SD) Median	Reached
Disease flares	To be predictor of an eczema flare. Biomarkers that can predict flare prior to the occurrence of clinical symptoms	80.8% 5.12 (1.18) 5	
Obstacle			
Independent validation	The results obtained in (often retrospective) research studies should be validated in adequately powered and prospectively ascertained patient cohorts	92.4% 5.92 (1.20) 6	
Harmonized data sources	To identify biomarkers, harmonized large data sources are needed. Having access to the data—namely molecular data from patient cohorts of sufficient size with detailed clinical characterizations—to support stratified analysis and initial biomarker discovery	73.1% 5.19 (1.63) 6	

AD = atopic Dermatitis, SCORAD = SCORing Atopic Dermatitis, EASI = Eczema Area and Severity Index, PASI = Psoriasis Area and Severity Index categorized according to their mean score (0.20—percentile = low priority, 0.60—percentile = medium priority; >0.6—percentile = high priority) dark green = high priority, middle green = medium priority, light green = low priority

diseases.³⁶ Although these obstacles did not reach agreement in round two of our study, they should not go unnoticed, and these recommendations will need to be revised over time.

The present study showed that the prediction of therapeutic response and disease progression are of high priority regarding high-quality AD and PSO biomarkers. The high mean score for therapeutic response in this study reflects the increasing importance of person-centered care for AD and PSO and the relevance of determining validated biomarkers for both providers and patients.

Strengths and limitations

The results of the present study should be interpreted under the consideration of several limitations. While a response rate of 70% is suggested for each Delphi round by Sumsion,²⁹ response rates of only 19.4% and 24.1% in rounds one and two were reached, respectively. Nevertheless, through the BIOMAP consortium, we were able to solicit expertise from a broad range of perspectives on an international level from research scientists, clinicians, pharmaceutical industry partners and patients to generate specific recommendations. Moreover, although there is no universal agreement on an optimal sample size for a Delphi study, the majority of Delphi studies have included 15 to 20 participants, and the panel's expertise is considered more important than its size. In addition, it should be noted that there is no universally applicable definition of agreement/consensus for the Delphi method. While some researchers state that 51% agreement on a statement could be considered acceptable,³⁷ others argue that 75%³⁸ to 100%³⁹ agreement is required. It should also be noted that even when the Delphi concludes that consensus has been achieved, it cannot be guaranteed that the final findings are the most appropriate and reliable end-point⁴⁰ and instead only indicate a majority opinion.⁴¹ However, major strengths of the present study are the systematic approach and the *a priori*

defined boundaries to generate the final recommendations based on the expertise of the research team and the state of art.

Conclusion

This study presents the first AD- and PSO-specific biomarker requirements through a Delphi survey of international experts. Developing a checklist that categorizes and prioritizes up-to-date requirements of biomarkers was an important step to improve future research and developments, which will foster the delivery of high-quality biomarkers applicable in research and daily clinical practice. Nevertheless, access to data and in particular molecular data from patient cohorts of sufficient size with detailed clinical characterizations is crucial to support stratified analysis and the discovery of future biomarkers.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

- 1 Laughter MR, Maymone MBC, Mashayekhi S *et al*. The global burden of atopic dermatitis: lessons from the global burden of disease study 1990–2017. *Br J Dermatol* 2021; **184**: 304–309.
- 2 Iskandar IYK, Parisi R, Griffiths CEM *et al*. Systematic review examining changes over time and variation in the incidence and prevalence of psoriasis by age and gender. *Br J Dermatol* 2021; **184**: 243–258.
- 3 Sacotte R, Silverberg JI. Epidemiology of adult atopic dermatitis. *Clin Dermatol* 2018; **36**: 595–605.
- 4 Lee HH, Patel KR, Singam V *et al*. A systematic review and meta-analysis of the prevalence and phenotype of adult-onset atopic dermatitis. *J Am Acad Dermatol* 2019; **80**: 1526–32.e7.
- 5 Abuabara K, Yu AM, Okhovat JP *et al*. The prevalence of atopic dermatitis beyond childhood: a systematic review and meta-analysis of longitudinal studies. *Allergy* 2018; **73**: 696–704.

- 6 Bylund S, von Kobyletzki LB, Svalstedt M et al. Prevalence and incidence of atopic dermatitis: a systematic review. *Acta Derm Venereol* 2020; **100**: adv00160.
- 7 Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. *J Eur Acad Dermatol Venereol* 2017; **31**: 205–212.
- 8 Kim J, Nadella P, Kim DJ et al. Histological stratification of thick and thin plaque psoriasis explores molecular phenotypes with clinical implications. *PLoS One* 2015; **10**: e0132454.
- 9 Eyerich K, Eyerich S. Immune response patterns in non-communicable inflammatory skin diseases. *J Eur Acad Dermatol Venereol* 2018; **32**: 692–703.
- 10 Weidinger S, Beck LA, Bieber T et al. Atopic dermatitis. *Nat Rev Dis Primers* 2018; **4**: 1.
- 11 Greb JE, Goldminz AM, Elder JT et al. Psoriasis. *Nat Rev Dis Primers* 2016; **2**: 16082.
- 12 Kahlenberg JM, Billi AC, Eyerich K et al. Biologics in the treatment of skin and rheumatologic diseases. *J Allergy Clin Immunol* 2020; **145**: 1138–1141.
- 13 AlQassimi S, AlBrashdi S, Galadari H et al. Global burden of psoriasis – comparison of regional and global epidemiology, 1990 to 2017. *Int J Dermatol* 2020; **59**: 566–571.
- 14 Germain N, Augustin M, Francois C et al. Stigma in visible skin diseases – a literature review and development of a conceptual model. *J Eur Acad Dermatol Venereol* 2021; **35**: 1493–1504.
- 15 Ring J, Zink A, Arents BWM et al. Atopic eczema: burden of disease and individual suffering – results from a large EU study in adults. *J Eur Acad Dermatol Venereol* 2019; **33**: 1331–1340.
- 16 Zink AGS, Arents B, Fink-Wagner A et al. Out-of-pocket costs for individuals with atopic eczema: a cross-sectional study in nine European countries. *Acta Derm Venereol* 2019; **99**: 263–267.
- 17 World Health Organization & International Programme on chemical safety. Biomarkers in Risk Assessment: Validity and Validation. Geneva: World Health Organization, 2001. <https://apps.who.int/iris/handle/10665/42363>
- 18 Renert-Yuval Y, Thyssen JP, Bissonnette R et al. Biomarkers in atopic dermatitis—a review on behalf of the international eczema council. *J Allergy Clin Immunol* 2021; **147**: 1174–90.e1.
- 19 Mulder MLM, van Hal TW, Wenink MH et al. Clinical, laboratory, and genetic markers for the development or presence of psoriatic arthritis in psoriasis patients: a systematic review. *Arthritis Res Ther* 2021; **23**: 168.
- 20 Laufer F, Baghin V, Standl M et al. Predicting persistence of atopic dermatitis in children using clinical attributes and serum proteins. *Allergy* 2021; **76**: 1158–1172.
- 21 Biomap. About BIOMAP. Towards Personalised Medicine for Inflammatory Skin Diseases. URL: <https://biomap-imi.eu/about> (last accessed 15 November 2021)
- 22 Plebani M, Zaninotto M, Mion MM. Requirements of a good biomarker: translation into the clinical laboratory. In van Eyk JE, Dunn MJ eds. Clinical Proteomics: From Diagnosis to Therapy. Weinheim: WILEY-VCH Verlag GmbH & Co. KGaA; 2008: 615–631.
- 23 Amgarth-Duff I, Hosie A, Caplan G et al. Toward best practice methods for delirium biomarker studies: an international modified Delphi study. *Int J Geriatr Psychiatry* 2020; **35**: 737–748.
- 24 Lassere MN. The biomarker-surrogacy evaluation schema: a review of the biomarker-surrogate literature and a proposal for a criterion-based, quantitative, multidimensional hierarchical levels of evidence schema for evaluating the status of biomarkers as surrogate endpoints. *Stat Methods Med Res* 2008; **17**: 303–340.
- 25 Henry NL, Hayes DF. Cancer biomarkers. *Mol Oncol* 2012; **6**: 140–146.
- 26 Graham B. Delphi as a method to establish consensus for diagnostic criteria. *J Clin Epidemiol* 2003; **56**: 1150–1156.
- 27 Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. *J Adv Nurs* 2000; **32**: 1008–1015.
- 28 FDA-NIH Biomarker Working Group. BEST (biomarkers, EndpointS, and other tools) Recourse [internet]. Silver Spring (MD): Food and Drug Administration (US); 2016. URL: <https://www.ncbi.nlm.nih.gov/books/NBK326791/> (last accessed 15 November 2021) Co-published by National Institutes of Health (US), Bethesda (MD)
- 29 Sumsion T. The Delphi technique: an adaptive research tool. *Br J Occup Ther* 2016; **61**: 153–156.
- 30 Tsoi LC, Rodriguez E, Stölzl D et al. Progression of acute-to-chronic atopic dermatitis is associated with quantitative rather than qualitative changes in cytokine responses. *J Allergy Clin Immunol* 2020; **145**: 1406–1415.
- 31 PsoBest. Das Deutsche Psoriasis-Register. URL: <https://www.psobest.de/das-register/> (last accessed 15 November 2021).
- 32 TREATGermany. Deutsches Neurodermitis-Register. URL: <http://www.treatgermany.org> (last accessed 15 November 2021).
- 33 MAPS. Munich Atopy Prediction Study. URL: <https://www.mri.tum.de/dermatologie> (last accessed 15 November 2021).
- 34 The BIOMAP Consortium. BIOMAP glossary. URL: <https://zenodo.org/record/4746584#.YPanEy1Q1MM> (last accessed 15 November 2021).
- 35 Broderick C, Christian N, Apfelbacher C et al. The BIOMarkers in atopic dermatitis and psoriasis (BIOMAP) glossary: developing a lingua franca to facilitate data harmonization and cross-cohort analyses. *Br J Dermatol* 2021; **185**: 1066–1069.
- 36 Aitken M, Villa P, Bennet K, Tewary V, Lech C. Optimizing oncology care through biomarker adoption: BARRIERS AND SOLUTIONS. IQVIA and the IQVIA Institution. 2020. URL: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/optimizing-oncology-care-through-biomarker-adoption.pdf?_=1636967483350 (last accessed 15 November 2021).
- 37 Loughlin KG, Moore LF. Using Delphi to achieve congruent objectives and activities in a pediatrics department. *J Med Educ* 1979; **54**: 101–106.
- 38 Keeney S, Hasson F, McKenna H. Consulting the oracle: ten lessons from using the Delphi technique in nursing research. *J Adv Nurs* 2006; **53**: 205–212.
- 39 Williams PL, Webb C. The Delphi technique: a methodological discussion. *J Adv Nurs* 1994; **19**: 180–186.
- 40 Keeney S, Hasson F, McKenna HP. A critical review of the Delphi technique as a research methodology for nursing. *Int J Nurs Stud* 2001; **38**: 195–200.
- 41 Rauch W. The decision Delphi. *Technol forecast soc change* 1979; **15**: 159–169.