The Alopecia Areata Consensus of Experts (ACE) study part II: Results of an international expert opinion on diagnosis and laboratory evaluation for alopecia areata

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Background: We previously reported the Alopecia Areata Consensus of Experts study, which presented results of an international expert opinion on treatments for alopecia areata.

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Objective: To report the results of the Alopecia Areata Consensus of Experts international expert opinion on diagnosis and laboratory evaluation for alopecia areata.

Methods: Fifty hair experts from 5 continents were invited to participate in a 3-round Delphi process. Consensus threshold was set at greater than or equal to 66%.

Results: Of 148 questions, expert consensus was achieved in 82 (55%). Round 1 consensus was achieved in 10 of 148 questions (7%). Round 2 achieved consensus in 47 of 77 questions (61%). The final face-to-face achieved consensus in 25 of 32 questions (78%). Consensus was greatest for laboratory evaluation (12 of 14 questions [86%]), followed by diagnosis (11 of 14 questions [79%]) of alopecia areata. Overall, etiopathogenesis achieved the least category consensus (31 of 68 questions [46%]).

Limitations: The study had low representation from Africa, South America, and Asia.

Conclusion: There is expert consensus on aspects of epidemiology, etiopathogenesis, clinical features, diagnosis, laboratory evaluation, and prognostic indicators of alopecia areata. The study also highlights areas where future clinical research could be directed to address unresolved hypotheses in alopecia areata patient care. (J Am Acad Dermatol 2021;84:1594-601.)

Key words: alopecia areata; assessment; consensus; Delphi; guideline.

INTRODUCTION

We previously reported the first part of The Alopecia Areata Consensus of Experts (ACE) study.[1] In ACE part II, we present international expert consensus on the pathogenesis, diagnosis, and laboratory evaluation of alopecia areata.

Treatment is influenced by a greater understanding of the pathogenesis of alopecia areata. ACE part II bridges theory to clinical practice. It considers the frequently posed questions by alopecia areata patients and, indeed, the general dermatologist. It aims to address the nuances often encountered in practice and be clinically relevant for the treating clinician.

CAPSULE SUMMARY

- This is the first large-scale international consensus on the diagnosis and laboratory evaluation of alopecia areata, to our knowledge.
- The consensus document identifies potential areas where research may be directed.

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Conflicts of interest: Dr Wall has received honoraria from Janssen, consultancy fees from Eli Lilly and Company, and travel fees and a grant from Pfizer; he has also received personal fees for consultancy from the nonprofit company National and International Skin Registry Solutions (NISR). Dr Blume-Peytavi has received honoraria and consultancies from Abbvie, Bayer, Galderma, Pfizer, Pierre Fabre Dermocosmetics, Sanofi, and Regeneron, none relevant to this work. Dr Callender is principal investigator for the Lilly Clinical Trial. Dr Cotsarelis is coinvestigator in a clinical trial sponsored by Lilly. Dr Craiglow has received honoraria and/or fees from Aclaris, Arena Pharmaceuticals, Pfizer, Regeneron, and Sanofi-Genzyme. Dr Eisman has been principal investigator in clinical trials for Pfizer Inc, AbbVie, Arena Pharmaceuticals, Boston Pharmaceuticals, Bristol-Myers Squibb, Botanix, Dermira, Eli Lilly and Company, Leo Pharma, Novartis, and Regeneron. Dr Farrant is a consultant for Lilly and principal investigator for Pfizer in clinical research studies. Dr Irvine has received honoraria and consultancies from Pfizer, Novartis, AbbVie, Sanofi, and Regeneron, none relevant to this work. Dr King is an investigator for Concert Pharmaceuticals Inc, Eli Lilly and Company, and Pfizer Inc; he is a consultant to and/or has served on advisory boards for Aclaris Therapeutics, Arena Pharmaceuticals, Bristol-Meyers Squibb, Concert Pharmaceuticals Inc, Dermavant Sciences, Eli Lilly and Company, and Pfizer Inc; he is on speaker's bureau for Pfizer Inc, Regeneron, and Sanofi Genzyme. Dr McMichael has received personal fees for consultancy work with Bioniz, Pfizer, and Revian, in addition to personal fees and grants from Aclaris, Concert, Galderma, Allergan, Almirall, Cassiopea, Incyte, Procter and Gamble, and Revian. Dr Messenger reports consultancies with Pfizer and Manentia. Dr Mirmirani has been an investigator for Concert Pharmaceuticals, Pfizer, and Eli Lilly and Company. Dr Olsen reports being an Aclaris investigator and Arena consultant. Dr Shapiro reports being a consultant and investigator for Pfizer and received an honorarium for consultancy for Pfizer and Lilly. Dr Sharma reports being a subinvestigator for Pfizer and Lilly. Dr Tosti reports being a consultant for DS Laboratories, Monat Global, Almirall, Tirthy Madison, Lilly, Leo Pharmaceuticals, Bristol Myers Squibb, and Proctor and

Abbreviation used:

ACE: Alopecia Areata Consensus of Experts

There remain many aspects of alopecia areata in which the available data are inconclusive. Consensus is defined by a general agreement among members of our expert panel, each of whom has exercised discretion in his or her decision making. For questions for which the threshold for consensus is achieved, few or none achieve unanimous agreement of the experts, and until conclusive data emerge, there will remain divergence of opinion. However, when taken together with current alopecia areata guidelines,[2-5] ACE part II provides additional insight into the current opinion from hair experts recognized in the field of alopecia areata.

METHODS

Expert panel selection

Fifty dermatologists with recognized expertise in hair and scalp disorders were invited to participate. Wide international representation was reflected in involvement from all 5 continents.

Delphi survey. The primary questionnaire was designed by a panel of 4 dermatologists. A systematic literature review was conducted to formulate questions to cover epidemiology, etiopathogenesis, diagnosis, laboratory evaluation, treatment, and prognosis of alopecia areata. Questions specifically included topics of clinical relevance, patient-directed questions (eg, those encountered in patient consultations), and some esoteric concepts.

The Delphi questionnaire was distributed with an online e-management survey system, Delphi Manager, maintained by the Core Outcome Measures for Effectiveness Trials initiative.[6]

Delphi process. The Delphi process has been validated in numerous studies to determine core outcomes[7] and define diagnostic criteria.[8,9] It was selected for ACE because it aims to achieve convergence of opinion through a series of rounds. Submitted answers are anonymized to minimize bias, whereas sequential iterations enable revision of judgment based on peer review to achieve consensus, when possible.[10-13]

ACE involved 2 questionnaire rounds followed by a final face-to-face meeting (Fig 1). For each questionnaire round, participants were instructed to assign a score for each question from 1 to 9 or "unable to score." A score of 1 corresponded to strong disagreement and 9 indicated strong agreement.

Consensus threshold. Threshold values have varied across Delphi studies.[7,8,14,15] Consensus threshold for ACE was set at greater than or equal to 66% agreement (scores 7-9) or disagreement (scores 1-3) of the participants scoring a given question or statement at round 1, round 2, or the face-to-face meeting but did not necessarily represent consensus of all 50 participants.

Questions with scores 4 to 6 were regarded as indeterminate. Questions excluded from the next round included those that had achieved consensus (≥66%) and those with a lack of consensus (≤33%), given the low probability that these would achieve consensus.

Questions included in the next round included those with consensus values between 33% and 66%.

Statistical analysis

R statistical software package (version 3.5.3; R Foundation for Statistical Computing [Vienna, Austria]) was used for data analysis.[16]

RESULTS

Expert panel

Of 50 invited hair experts, 41 (82%) completed round 1 and 39 (78%) round 2, and 30 (60%) attended the face-to-face meeting at the 11th World Congress for Hair Research in Sitges, Spain. Thirty-six experts (88%) routinely managed adults and children with hair loss disorders. Twenty-three individuals (56%) work in public (academic

Gamble. Dr Sinclair has served as a consultant or paid speaker for, or participated in clinical trials sponsored by, Leo Pharma, Amgen, Novartis, Merck & Co, Celgene, Coherus Biosciences, Janssen, Regeneron, MedImmune, GlaxoSmithKline, Cutanea, Samson Clinical, Boehringer Ingelheim, Pfizer, MSD, Oncobiologics, Roche, Eli Lilly and Company, and Bayer. Drs Asz-Sigall, Bergfeld, Betz, Combalia, Donovan, Grimalt, Harries, Hordinsky, Itami, Lee, Orlow, Piraccini, Rakowska, Reygagne, Roberts, Rudnicka, Vogt, Yip, and Zlotogorski, and Authors Meah, York, Bhoyrul, Bokhari, Chitreddy, Green, Jolliffe, and Wade have no conflicts of interest to declare.

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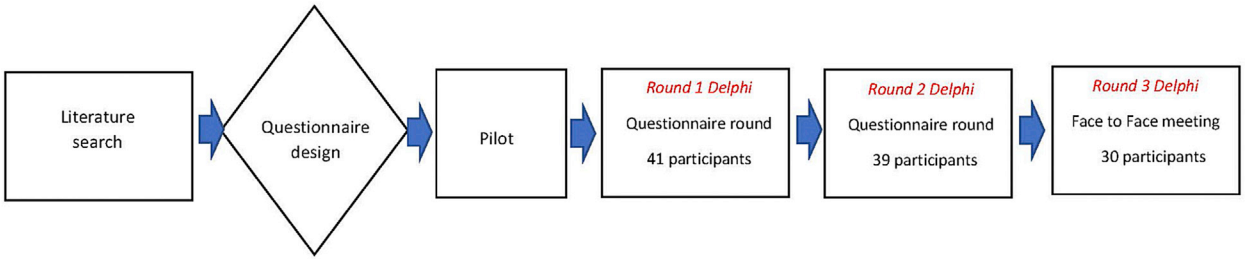

Fig 1. The Delphi process in the Alopecia Areata Consensus of Experts study.

institutions) and private practice, 13 (32%) exclusively in private practice, and 5 (12%) exclusively in public practice. Participants were from Europe (15; 37%), Asia (3; 7%), Australia (9; 22%), and North America (14; 34%).

Delphi rounds

Fig 2 summarizes the ACE Delphi rounds. One hundred forty-eight questions related to epidemiology, etiopathogenesis, clinical features, diagnosis, laboratory evaluation, prognosis, and prognostic indicators. Expert consensus was achieved in 82 questions (55%), including 10, 47, and 25 questions after rounds 1, 2, and 3, respectively. The category with the greatest consensus was laboratory evaluation (12 of 14 questions [86%]), followed by diagnosis (11 of 14 questions [79%]). The least consensus achieved was for etiopathogenesis (31 of 68 questions [46%]).

CONSENSUS OUTCOME

Epidemiology

Six questions related to epidemiology. Consensus was achieved in 3 questions (50%).

- Ethnicity (race) does not alter the natural history/prognosis of alopecia areata.
- Neither ethnicity nor climate/geographic latitude influences the risk of a poor response to treatment.

Etiopathogenesis

Sixty-eight questions related to etiopathogenesis, subdivided into family history, genetics, autoimmune disease, allergic comorbidities, associated comorbidities, nutritional, stress, and environmental. Consensus was achieved in 31 questions (46%).

- Factors that were considered to increase the risk of developing alopecia areata included a family history of alopecia areata/organ-specific autoimmune disease; genotype; and a personal history of autoimmune disease, thyroid disease, vitiligo, atopy, or atopic dermatitis. Iron deficiency and pregnancy were not considered to increase the risk of developing alopecia areata.
- Factors that were considered to influence the natural history/prognosis of alopecia areata included genotype and a personal history of autoimmune disease or atopy. Iron deficiency and vaccination were not considered to influence the natural history or prognosis of alopecia areata.
- Factors that were considered to trigger initial disease and episodic relapse(s) included genotype with environmental trigger, major traumatic life event, and acute stress.
- Factors that were considered to influence the response to treatment included genotype. Iron deficiency and vaccination were not considered to influence the response to treatment.

Clinical features

Consensus was achieved in 11 of 23 questions (48%) regarding clinical features:

- Signs indicating disease activity include exclamation mark hairs, trichoscopic black dots, a positive hair pull test result, and anagen effluvium.
- Severity of Alopecia Tool score plus quality of life (eg, Dermatology Life Quality Index score) or Severity of Alopecia Tool score plus scalp surface area plus quality of life are required in clinical trials involving adults or children.
- Severity of Alopecia Tool score is a sufficient measure of disease extent in clinical practice in adults and children.

Diagnosis

Consensus was achieved in 11 of 14 questions (79%) relating to the diagnosis of alopecia areata:

- Alopecia areata diagnosis can be determined by clinical examination and trichoscopic findings.
- Hair pluck trichograms are not useful in the diagnosis of alopecia areata.
- Scalp biopsy is indicated in the following circumstances: a solitary patch recalcitrant to treatment,

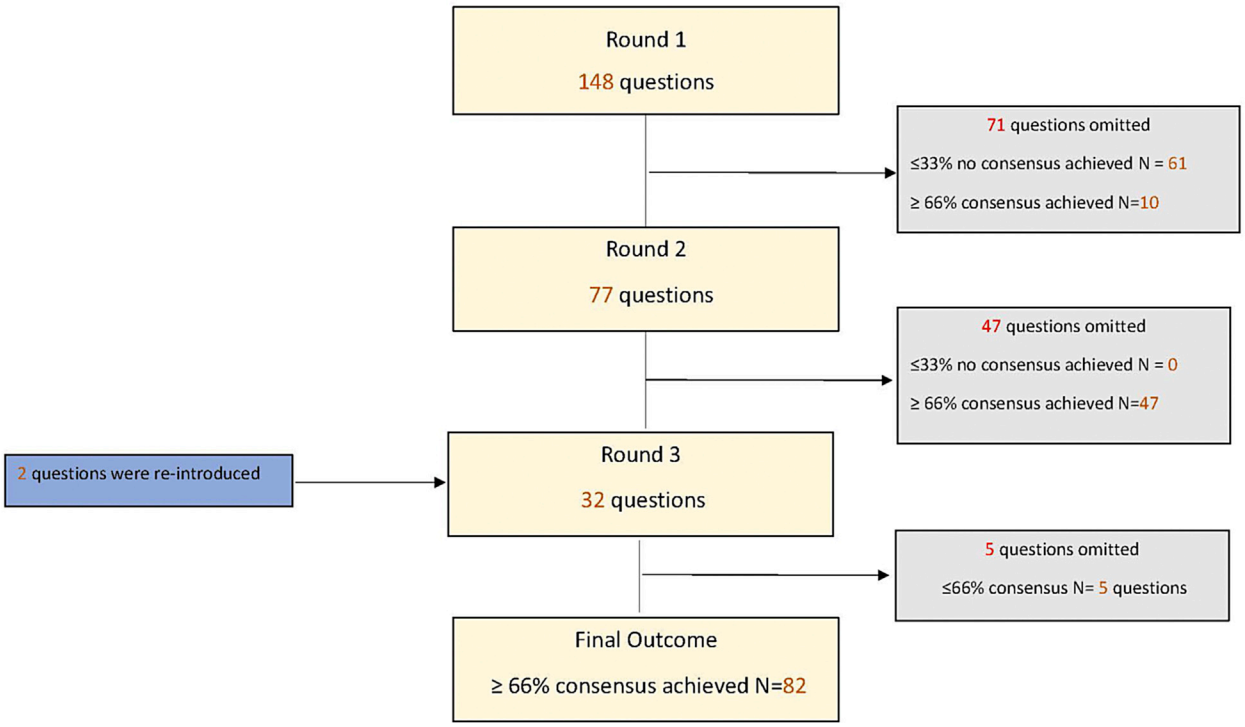

Fig 2. Summary of results from all Delphi rounds: Alopecia Areata Consensus of Experts part II.

diffuse alopecia, and when cicatricial alopecia cannot be excluded clinically.
- When scalp biopsies are performed in alopecia areata, it is usually sufficient to take 1 biopsy (for horizontal and vertical sectioning) to confirm the diagnosis of alopecia areata, but occasionally 2 or more biopsies (for horizontal and vertical sectioning) may be needed.
- Biopsy site should be from the edge of a lesion (not the center), and preferably from a lesion located at a site normally resistant to androgenetic alopecia (eg, occipital scalp).
- An additional scalp biopsy from nonlesional scalp is not considered important.

Laboratory evaluation

Consensus was achieved in 12 of 14 statements (86%) regarding laboratory evaluation of alopecia areata:

- Fungal microscopy should not be performed routinely and is required only when there is clinical suspicion of tinea capitis.
- Routine blood tests (complete blood cell count; renal and liver function) and screening for autoimmune disease, connective tissue disease, celiac disease, pernicious anemia, and diabetes are not required and should not be performed for all patients at the diagnosis of alopecia areata.
- In the absence of relevant clinical symptoms and signs, viral serology is not useful to identify a potential alopecia areata episode trigger.
- Early-morning cortisol level is not a useful test in patients who believe stress may have triggered an alopecia areata episode.
- Before initiation of systemic treatment of alopecia areata, investigation is identical to requirements for other dermatologic diseases.

Prognosis and prognostic indicators

The effect of disease duration and disease phenotype on alopecia areata progression was addressed. Poor prognosis in this context referred to developing a severe disease phenotype but did not imply being refractory to treatment; and response to treatment was queried separately. Consensus was achieved in 14 of 23 questions (61%).

- Prognosis is worse when alopecia areata persists beyond 5 years.
- Hair loss can become irreversible when alopecia areata persists for 10 years but should not be assumed to be so or contraindicate a trial of therapy.
- Development of lesions of alopecia can be influenced by systemic factors (eg, metabolic [hormones] and immunologic [proinflammatory cytokines] factors).

Table I. Nonconsensus outcomes for Alopecia Areata Consensus of Experts part II

Category	Disagreement among the experts regarding the following statements
Epidemiology	Ethnicity (race) influences the risk of developing AA.
	Climate/geographic latitude influences the risk of developing AA and influences the natural history/prognosis of AA
Etiopathogenesis	Factors that were considered to increase the risk of developing AA: family history of atopy, vitamin D deficiency, viral illness and vaccination
	Factors that were considered to increase the risk of developing AT/AU: family history of organ-specific autoimmune disease/atopy, vitamin D deficiency and viral illness
	Factors that were considered to influence the natural history/prognosis of AA: family history of AA/organ-specific autoimmune disease/atopy, vitamin D deficiency, pregnancy and viral illness
	Factors that were considered to trigger initial disease and episodic relapse(s): chronic stress
	Factors that were considered to influence response to treatment: family history of AA/organ-specific autoimmune disease/atopy; personal history of autoimmune disease, type 1 diabetes, myasthenia gravis, pernicious anemia, psoriasis, lupus, rheumatoid arthritis, celiac disease, atopy, asthma, allergic rhinoconjunctivitis, food allergy, allergic contact dermatitis; pregnancy; vitamin D deficiency and viral illness
	Alopecia areata can be seasonal (regardless of geographic location) or cyclic (eg, same month every year).
Clinical features	Signs that indicate disease activity (in addition to disease spread): telogen effluvium; scalp itch, tingling, dysesthesia; trichoscopic yellow dots
	Outcome measures for clinical trials: • SALT score is a sufficient measure of disease extent in adults and children. • SALT score + SSA is required to measure disease severity in children.
	Outcome measures for clinical practice: • SALT score + SSA is required to measure disease severity in adults and children. • SALT score + QoL (eg, DLQI) is required to measure disease severity in adults and children. • SALT score + SSA + QoL is required to measure disease severity in adults and children.
Diagnosis	The optimal method of scalp biopsy is a single scalp biopsy sectioned horizontally or a single biopsy sectioned vertically.
	Trichograms are useful in the assessment of disease activity in AA.
Laboratory evaluation	Routine screening blood tests should be performed for vitamin D deficiency and thyroid disease.
Prognosis and prognostic indicators	Active treatment early in the disease affects prognosis.
	Prognosis is worse when AA persists beyond 6 to 12 mo.
	Hair loss can become irreversible when AA persists for <6 mo, 12 mo, 5 y, or 8 y.
	Development of lesions of alopecia can be influenced by local factors.
	Trachyonychia alters response to treatment.

AA, Alopecia areata; *AT*, alopecia totalis; *AU*, alopecia universalis; *DLQI*, Dermatology Life Quality Index; *QoL*, quality of life; *SALT*, Severity of Alopecia Tool; *SSA*, Scalp Surface Area.

- Ophiasis phenotype indicates poor prognosis.
- Eyebrow, eyelash, and nonscalp hair loss indicates poor prognosis.
- Nail pitting suggests an increased risk of developing alopecia totalis (AT)/alopecia universalis (AU), worsens alopecia areata prognosis, and reduces response to treatment.
- Trachyonychia suggests an increased risk of developing AT/AU and worsens alopecia areata prognosis.

NONCONSENSUS OUTCOME

Table I summarizes nonconsensus outcomes. Consensus was not achieved in 66 questions (45%): 61, 0, and 5 questions after rounds 1, 2, and 3, respectively.

DISCUSSION

To our knowledge, ACE part II represents the largest international expert consensus study on the diagnosis and laboratory evaluation for alopecia areata achieved via the Delphi process.

Consensus was achieved for genotype increasing the risk of developing alopecia areata, affecting the prognosis of alopecia areata, and influencing the response to treatment of alopecia areata. Alopecia areata is considered a complex polygenic disorder and the genetic etiology is well described. A positive

family history is reported in 20% to 40% of cases[17] and twin studies have shown high concordance (42%) among monozygotic twins.[18] The first alopecia areata genomewide association study identified 8 regions in the genome associated with alopecia areata,[19] increasing to 14 susceptibility loci in later studies.[20]

Acute stress was recognized as a trigger for initial disease and episodic relapse(s) of alopecia areata. However, tests to confirm a stress trigger (eg, early-morning cortisol level) are not useful. Experimental studies have shown increased expression of hypothalamic-pituitary-adrenal hormone receptors (eg, corticotrophin-releasing hormone receptor 2,[21] adrenocorticotropin,[22] and estrogen receptor 1) in lesional alopecia areata hair follicles.[23] There was no consensus on the role of chronic stress as a disease trigger.

Consensus was achieved on the recording of Severity of Alopecia Tool score as a measure of disease activity both in clinical practice and clinical trials in children and adults. It was acknowledged that additional assessments (scalp surface area and quality of life) are required for the purpose of clinical trials. The Severity of Alopecia Tool has been validated in several alopecia areata studies for use in clinical trials and routine practice. Additional measures such as Alopecia Density and Extent score[5] have also been proposed.

There was agreement on the site of scalp biopsy. The statement concerning the number of scalp biopsies—2 or more biopsies (for horizontal and vertical sectioning)—for the histologic diagnosis of alopecia areata was discussed again at the face-to-face meeting after a specific request to revisit this was accepted. It was agreed that horizonal and vertical sectioning is important to confirm the histologic diagnosis of alopecia areata, and that a single biopsy (sectioned horizontally and vertically) is usually sufficient to confirm the diagnosis of alopecia areata but that in some instances more than 1 biopsy may be needed. Experts thought that clarity on this was essential because a question specifically on whether performing a single biopsy (sectioned horizontally and vertically) was sufficient for the diagnosis of alopecia areata was not included in the questionnaire.

Consistent with current recommendations,[5] diffuse alopecia areata may also necessitate a biopsy. Additional investigations to exclude alopecia areata mimickers (eg, tinea capitis) are indicated only when there is clinical uncertainty. The expert group agreed that autoimmune screening investigations are not required for all alopecia areata patients; however, there was no consensus on testing specifically for vitamin D and thyroid disease. In patients with symptoms suggestive of coexisting autoimmune disease, appropriate testing will still be required.

There was consensus on worsening prognosis if alopecia areata persists beyond 5 years. Ikeda[24] proposed 12 months, and the current expert opinion is perhaps a reflection on treatment progress since the author's historical observations in 1965.

Although disease duration of greater than 10 years may lead to irreversible hair loss, recommendations were not to exclude such patients from active treatment when available.

Nail disease, particularly pitting, was recognized as a poor prognostic finding with respect to developing a severe disease phenotype and affecting response to treatment. Trachyonychia may also act as a poor prognostic marker but there was no consensus on whether it affects response to treatment. Treatment success of trachyonychia has been reported.[25]

ACE part II identified 66 nonconsensus questions. The majority (61) emerged after round 1 of the Delphi process and all with less than 33% consensus. This indicates wide divergence in opinion for these questions. The significant number of questions from etiopathogenesis and prognosis suggests that there is still much to learn, and whilst data emerge and research informs, viewpoints may eventually merge.

There are potential limitations to consider. First, although there was wide international participation and involvement of academic and community hair experts, there was low expert representation from Africa (n = 1), South America (n = 0), and Asia (n = 3), and overrepresentation from Europe (n = 15) and North America (n = 14). Second, the involvement of a hair scientist in the initial design of the questionnaire to provide an additional perspective on alopecia areata pathogenesis might have been beneficial. Third, not all participants answered each question when it was presented the second or third time and 60% (30) attended the final face-to-face meeting in Sitges. Fourth, as previously reported,[1] time constraints to cast votes at the final face-to-face meeting, and influencer bias because the meeting was not chaired by an independent nonvoting individual, are further possible limitations.

CONCLUSION

In summary, ACE part II has provided insight into areas where current expert opinion is divided and where future research could be directed (eg, etiopathogenesis of alopecia areata). As we learn more about alopecia areata, the divergence may narrow, but in doing so we are hopeful that ACE part II will provide a useful framework for dermatologists,

health care providers, and scientists alike, so that ultimately the greatest beneficiaries are our alopecia areata patients. Moreover, ACE has identified the need for an international alopecia areata registry, development of which will enable recording of comparable, robust, real-world data to better inform on the prognostic significance of alopecia areata.

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