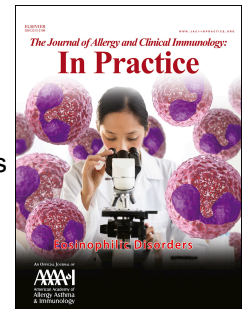


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**Differences in the Evaluation of Skin Prick Testing Results for Food Allergy Diagnosis
Between US and UK Physicians.**

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Trust, London, UK.

Clinical Implications: We have identified significant discordances in SPT interpretation between
allergists in the US and the UK, which may lead to conflicting diagnoses for patients.

Standardizing SPT measurement and interpretation for the evaluation of food allergy in different
countries is important.

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Conflict of Interest:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The diagnosis of IgE-mediated food allergy is based on symptoms of an allergic reaction within 2 hours of an inciting event and is confirmed by diagnostic tools such as skin prick testing (SPT) and serum specific IgE. The decision to proceed with oral food challenges, the gold standard for validating IgE-mediated food allergies, depends on the clinical history, SPT, and IgE testing results. Since the late 19th century, SPT has assisted the diagnosis of IgE-mediated reactions to allergens with high sensitivity and specificity.

SPT evaluates the host's physiologic reaction to an allergen by producing a wheal and flare. This response depends on the presence of IgE antibodies, functional mast cells, and reactive bystander tissue cells. The wheal and flare reaction can be ascribed to various compounds released by activated mast cells. (1) Histamine causes plasma extravasation (wheal reaction) and vasodilation (flare response). Eicosanoids (leukotrienes and prostaglandins) contribute to the erythematous response.(2) Patient age may affect SPT results: young infants have hypoactive histamine responses, and these infants show larger flare and smaller wheal responses.(3)

Multiple "scarification" devices were developed over the years to perform SPT (*e.g.*, the Mueller device, Hagerdorn cutting needle, multitest device, etc.). Although devices have improved over time, quantifying the observed reaction has consistently relied on measuring the wheal that forms in the area the device was used. It is generally accepted that a wheal diameter response of ≥ 3 mm above the saline negative control is considered positive in SPT, but there is no global consensus on the practical consideration of the flare (erythematous) response. Our work aims to examine differences in how allergists in the United States (US) and the United Kingdom (UK) evaluate SPT results in the context of IgE-mediated food allergy diagnosis.

79

80 We developed an electronic survey questionnaire to evaluate the interpretation of SPT for the
81 diagnosis of IgE-mediated food allergy (**Table 1**). The brief, four-question survey was circulated
82 via two national allergy/immunology societies (American College of Allergy, Asthma and
83 Immunology [ACAAI] and British Society of Allergy and Clinical Immunology [BSACI]) to
84 allergy specialists in the US and the UK, in 2017 and 2018, respectively. The survey was
85 reviewed and approved by both societies prior to circulation. All responses were confidential
86 and did not contain any identifiers. Data were analyzed using contingency tables and Chi-Square
87 Test or Fisher-exact *t*-test statistics.

88

89 The survey was circulated to active members of the relevant societies; 970 allergists in the US
90 and 351 in the UK. The total number of responders were $n=478$ (49%) in the US and $n=159$
91 (45%) in the UK (**Table 1 & Figure 1**). The respondent rate was similar to previous published
92 reports using survey questionnaires submitted through professional allergy societies (4). The survey
93 results revealed that when evaluating SPT for IgE-mediated food allergy, 82% (391/474) of US
94 allergists measure both the wheal and the flare compared to only 14% (23/159) of UK allergists
95 ($p<0.01$). More UK allergists ignore the flare in the absence of the wheal (79 vs 69 %, UK vs
96 US; $p=0.02$). Fifty-eight percent of US allergists will consider a positive flare response in the
97 absence of a wheal, and 24% will consider a >10 mm flare response as positive. In contrast, only
98 22 % of UK allergists will consider a positive flare response ($p<0.01$, vs US) in the absence of a
99 wheal. Finally, the provider's practice with regards to measuring and considering the flare did
100 not change over time in either region based on self-report (82% vs 84%, US vs UK; $p=0.63$).

101

SPT is a widely used tool in the diagnosis of IgE-mediated food allergy.(5)(6) Accurate measurement and consistent interpretation of the SPT response is crucial, and the use of standardized metrics to interpret SPT positivity has important clinical implications. We surveyed allergists in the US and UK and found that there were significant discrepancies in the evaluation of SPT results between the two geographical regions, mostly related to flare measurement and interpretation. The differences largely reflect regional expert opinion standards and guidelines.(7)(8)(9) Specifically in 2008, the US Joint Task Force on Practice Parameters, comprised of members from two professional allergy societies, the American Academy of Allergy Asthma and Immunology (AAAAI) and the ACAAI, recommended that “objective wheal-and-flare responses be recorded in millimeters (diameter or area)” (7) and “a positive SPT test is considered a wheal that is 3mm or greater in diameter than the negative control with 10mm or more of surrounding erythema or flare.” In contrast, European guidelines recommend using only wheal measurements to evaluate the SPT response: “the largest diameter of the wheal of each particular test is measured, a positive being a wheal of ≥ 3 mm.” (9) The BSACI states on SPT: “measure the longest extent of the wheal (not including the flare) and the extent 90° to the first measurement.” (www.bsaci.org). Currently, there is no consensus expert opinion on the utility and prognostic value of measuring SPT flare reactions in the evaluation of food allergy.

Overall, SPT is a benchmark quantitative scoring system that can assist medical decision-making in the diagnosis of food allergy. Our survey has identified significant discordances in SPT interpretation practices between allergists in the US and the UK. These differences may lead to conflicting diagnoses for patients, alter management plans, and ultimately affect the clinical outcomes of food-allergic patients. We noted with interest that, while 83% of US allergists

measure the flare, it is unclear how this measurement is used, given that only 30% consider it meaningful in the absence of a wheal. Our work underscores the importance of standardizing SPT measurement and interpretation for the evaluation of food allergy in different countries.

There are certain limitations in our study. We did not elicit if SPT interpretation affected a practitioner's decision to proceed with oral food challenges. Our survey did not include clinical scenarios which would give insight into differences in the medical decision-making process and the questions did not address whether the practice of using wheal +/- flare was applied across all age groups tested for food allergy. Similarly, we did not inquire how practitioners would interpret histamine control reactions if there was no flare associated with the wheal. We also did not ask about different devices that may have been used. Lastly, we do not know whether the respondents in each region disproportionately represented academia versus private practice or any particular geographic region.

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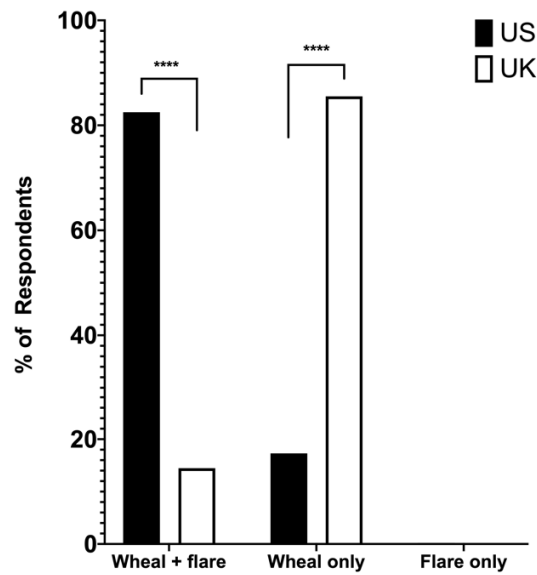
Table 1: Survey questions

Figure 1. Percentage of US and UK allergist respondents to the electronic questionnaire.

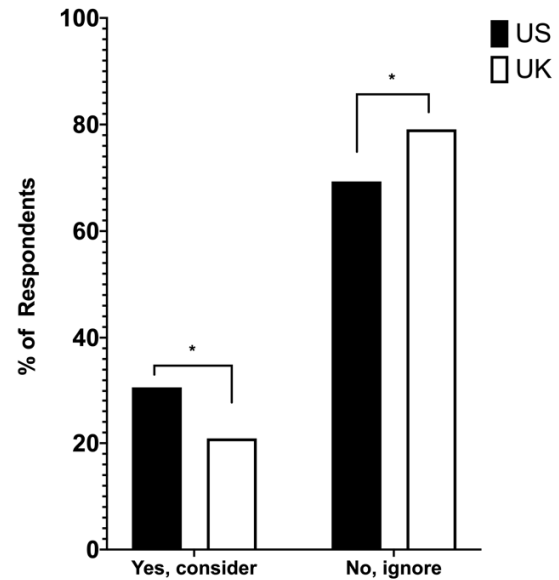
Statistical significance was determined at the * $p < 0.02$, ** $p < 0.01$, *** $p < 0.001$, and **** $p < 0.0001$ levels.

Table I. Survey Questions	Respondents Number [% of Total]		P-value
	US	UK	
Q1: Do you measure both wheal and flare when skin prick testing for food allergy? A) <i>Yes, I measure both.</i> B) <i>No, I measure the wheal.</i> C) <i>No, I only measure the flare.</i>	N = 474 391 [82.5] 82 [17.3] 1 [0.2]	N = 159 23 [14.5] 136 [85.5] 0 [0]	<0.0001 <0.0001 0.56
Q2: If the wheal diameter is 0 mm (= there is no visible wheal), do you consider a large flare response as a positive result for skin prick testing? A) <i>Yes, I will consider a large flare response (in the absence of a wheal) as a positive skin testing result.</i> B) <i>No, if the wheal is absent, I will ignore the flare.</i>	N = 476 146 [30.7] 330 [69.3]	N = 158 33 [20.9] 125 [79.1]	0.02 0.02
Q3: What cut-off do you use for a positive flare response? A) <i>None, I ignore/don't measure the flare.</i> B) <i>I consider a >5 mm flare response positive.</i> C) <i>I consider a >10 mm flare response positive.</i> D) <i>I consider a >15 mm flare response positive.</i> E) <i>I consider any diameter of flare response positive.</i>	N = 464 195 [42.0] 77 [16.6] 110 [23.7] 37 [8.0] 45 [9.7]	N = 157 123 [78.3] 16 [10.2] 11 [7.0] 1 [0.6] 6 [3.8]	<0.0001 0.05 <0.0001 <0.001 0.02
Q4: Has your practice with regards to measuring/considering the flare response changed over the years? A) <i>No, I have always practiced this way.</i> B) <i>Yes, I now take the flare response into account.</i> C) <i>Yes, I now ignore the flare response.</i>	N = 477 393 [82.4] 58 [12.2] 26 [5.5]	N = 159 134 [84.3] 14 [8.8] 11 [6.9]	0.58 0.25 0.49

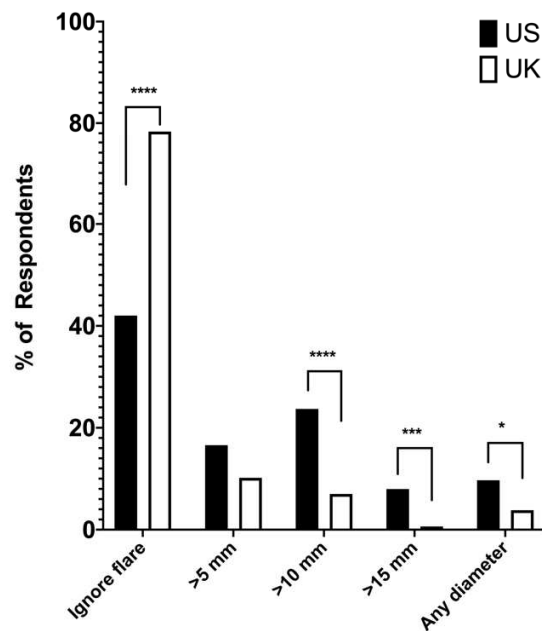
Q1: Do you measure both wheal and flare when skin prick testing for food allergy?



Q2: If the wheal diameter is 0 mm (= there is no visible wheal), do you consider a large flare response as a positive result for skin prick testing?



Q3: What cut-off do you use for a positive flare response?



Q4: Has your practice with regards to measuring/considering the flare response changed over the years?

