

Dubiously Doubtful: An Exploration of the Literature Concerning Doubtful, Macular Erythema, “?+,” and “+/-” Patch Test Reactions

Kevin K. Veverka, MD* and Mark D. P. Davis, MD†

When the final patch test reading is barely discernable, it is termed a doubtful, *macular erythema*, “?+,” or “+/-” reaction (hereby referred to as *doubtful reaction*). Information is conflicting about how to interpret doubtful reactions. Many guidelines do not comment on how to approach doubtful reactions; others state that further evaluation can (not should) be performed. In clinical reports, some investigators regard them as positive allergic reactions; some, as positive under certain circumstances; and many, as negative. Indeed, 16 (84%) of 19 recent reports of patch test reactions to standard/baseline series considered doubtful reactions negative for purposes of the report and did not include the number of these reactions. The problem is that these reactions are common and are not infrequently relevant. We recommend that researchers include frequency of doubtful reactions in reports and that doubtful reactions be assessed with the same scrutiny as stronger allergic reactions in the clinical setting.

Doubtful (also termed *macular erythema*, “?+,” or “+/-”) reactions are difficult reactions to assess. They represent a recognizable elephant in the room of patch testing because, although they are common, they are rarely mentioned or discussed in studies. We aimed to review the literature to understand how frequent doubtful patch test reactions are noted and how doubtful reactions are interpreted in both the clinical and the academic settings. Using PubMed, we performed a literature search to assess the published guidelines and epidemiologic reports of patch test reactions. Despite that some guidelines advocate the clinical relevance of doubtful patch test reactions, most studies ignore or do not report these reactions. There is evidence to suggest that doubtful reactions should be viewed in the clinical setting with the same analysis for relevance as stronger reactions.¹⁻³

Patch testing is the criterion standard for the determination of which allergen may be causing allergic contact dermatitis. In general, patches that contain a set of allergens are placed on day 1 of testing and are removed on day 3. Generally, on day 3 and days 5 to 8 of testing, the area is evaluated for reactions, and readings of the final reactions are graded. (These days are classified as days 0, 2, and 4 by the International Contact Dermatitis Research Group [ICDRG].) According to the ICDRG, the reaction is then categorized as negative

(-); irritant (IR); doubtful (by other groups, these are called *macular erythema*, “?+,” or “+/-” reaction); weak, containing nonvesicular erythema with infiltration or papules (referred to as + or 1+); strong, containing vesicles or edema (referred to as ++ or 2+); or extreme, with bullous, ulcerative, or spreading outside the areas of contact (referred to as +++ or 3+).⁴ It is universally accepted that the 1+, 2+, and 3+ reactions may be consistent with allergic-type reactions, but discord continues about the evaluation of doubtful reactions.⁵⁻⁷

Different patch test groups use various terms for slightly detectable patch test reactions: doubtful macular erythema, “?+,” or “+/-” reactions. In this article, we use the term *doubtful* for patch test reactions interpreted as macular erythema, “?+,” or “+/-” reactions or doubtful patch test reactions. There is little in the literature that describes the doubtful patch test reaction. In the present study, we reviewed the literature about doubtful reactions, including guidelines for their interpretations, how they are viewed in epidemiologic studies, and how studies report the relevance and clinical management of these reactions.

METHODS

Patch Test Interpretation Guidelines

With use of PubMed (National Library of Medicine), a literature search was performed to identify published guidelines from national and multinational dermatologic and contact dermatitis societies with regard to the suggested interpretation of patch test reactions. We included articles written in the English language and published through December 2018. Search terms were combinations of “patch test,” “allergic contact dermatitis,” “guidelines,” “doubtful,” “questionable,”

From the *Department of Internal Medicine, MacNeal Hospital, Berwyn, IL; and †Department of Dermatology, Mayo Clinic, Rochester, MN.

Address reprint requests to Mark D. P. Davis, MD, Department of Dermatology, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail: davis.mark2@mayo.edu.

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“interpretation,” “baseline series,” and “standard series.” The abstracts and the full-text articles were reviewed to assess for eligibility.

Epidemiologic Factors and Interpretation of Patch Test Reactions

With use of PubMed (National Library of Medicine), a literature search was performed to identify epidemiologic studies of patch test reactions to a standard allergen series performed by group practices and studies of the interpretation of patch test reactions. The studies were written in the English language and published from the time of our group's previous report,⁵ March 2005 to December 2018. Abstracts and full-text articles were reviewed to assess for eligibility. The studies were included if their methods section explicitly stated or referred to another article that plainly defined the reaction types that constituted a positive reaction. For groups with more than 1 report, only the most recent study was reviewed.

Statistical Analysis

A 2-sided *t* test was performed, with a statistical significance level at $P < 0.05$, in the comparison of the rate of positive reactions among the studies with doubtful reactions categorically considered *negative* and the studies with doubtful reactions considered *positive* if relevant.

RESULTS

Patch Test Interpretation Guidelines

Practice guidelines for patch testing are followed by most providers performing patch testing. An online survey was reported of 169 providers who performed patch tests and who represented 47 countries, including allergists and dermatologists.⁸ Among the respondents who routinely performed patch tests, 99 (83%) of 119 stated that they used clinical guidelines in practice.

The most commonly referenced guideline was the American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology (AAAAI/ACAAI) 2006 report (32%),⁶ followed in frequency by the European Network on Drug Allergy/European Academy of Allergy and Clinical Immunology Drug Allergy Interest Group⁹ (24%) and the ICDRG 1970 criteria for patch test reading (18%).⁴ Marked variability was observed in the guidelines referenced by the geographic location of the survey respondent.

The oldest study referenced in that study⁸ was from the ICDRG in 1970, which established the system of patch test readings (ie, of -, IR, ?+, +, ++, and +++).⁴

In Table 1, we summarize the guidelines regarding doubtful (?+) patch test reactions identified in the literature search. In summary, some guidelines recommend that doubtful reactions should not be categorically negative but rather may warrant further evaluation by the patch test provider. Regarding doubtful reactions, the German Dermatologic Society¹¹ suggests that further workup can be performed, whereas the European Society of Contact Dermatitis¹³

advises that “further investigations may have to be performed.” The AAAAI/ACAAI⁶ specifically advise consideration of repeated open application test (ROAT). By comparison, the American Academy of Dermatology¹⁰ guidelines and the British Association of Dermatology¹⁴ continue to be mute on the subject of further workup of these reactions.

Of note, the group statement of the North American Contact Dermatitis Group (NACDG) in their most recent report¹² recommends taking the patient's entire reaction profile to help ascertain the significance of doubtful reactions. The example given by the NACDG is a doubtful reaction to a formaldehyde-releasing agent in the setting of stronger allergic reactions (or lack thereof) to other formaldehyde-releasing agents.¹⁵

Studies Reporting the Results of Patch Testing

The present review identified 19 studies published from March 2005 to December 2018 that reported reactions to a baseline or standard series. All the studies included were 1-time reports and did not include the results of long-term follow-up. Of these studies, 16 (84%) categorized doubtful reactions as negative, regardless of relevance.¹⁶⁻³¹ The geographic breakdown of these studies is as follows: Asia (n = 8 [53%]), Australia (n = 1 [7%]), Europe (n = 5 [33%]), North America (n = 1 [7%]), and South America (n = 1 [7%]). Three studies (16%) considered doubtful reactions to be positive (allergic) if the reactions were determined to be relevant.^{15,32,33} The geographic breakdown of these 3 studies is as follows: Africa (n = 1 [33%]) and North America (n = 2 [67%]).

In the studies with doubtful reactions categorized as negative, the percentage of patients with at least 1 positive patch test reaction ranged from 19.3% to 85.6% (mean, 55.9%; median, 55.4%). In studies with doubtful reactions categorized as positive if they were determined to be relevant, the percentage of patients with at least 1 positive patch test reaction ranged from 52.7% to 66.6% (mean, 61.8%; median, 66.0%). No significant difference was seen in the reaction rates between the 2 groups ($P = 0.67$).

Questions About Doubtful Reactions

How Common Are Doubtful Patch Test Reactions?

Because doubtful (very mild/doubtful/macular erythema/?+/-) reactions are interpreted as negative in most reports, little information is available about how common they are. Mayo Clinic reported its experience with patch testing to a standard series and concluded that doubtful (macular erythema) reactions are common and may be of clinical relevance⁵: 42.4% of patch test reactions were graded as doubtful.

Could Doubtful Patch Test Reactions Be Relevant?

In the same report from Mayo Clinic,⁵ grading physicians believed that 78.8% of reactions categorized as doubtful were at least of possible relevance. In 2008, Devos et al¹ found that 25.0% of doubtful reactions to fragrance mix were relevant. Among the patients who had repeated patch tests, 43.5% had a positive reaction

TABLE 1. Patch Test Guidelines for Doubtful Reactions

Patch Test Group	Year	Recommendation	Citation
American Academy of Dermatology	1995	"? (+ or –) reaction = weak erythema only... doubtful existence of contact allergy." No further mention of how to categorize this reaction or specific follow-up testing.	Drake et al ¹⁰
German Dermatologic Society	2008	"If test results are doubtful the test can be repeated, however not before complete resolution of all reactions of the first test. Based on clinical experience, an interval of about 2 months should be sought."	Leitlinien der Deutschen Dermatologischen ¹¹
ICDRG	2009	"Doubtful reactions may be clinically relevant according to undeniable clinical criteria or follow-up testing. It could be worthwhile to ascertain whether doubtful (?) or weak (+) patch test reactions yield a significantly different relevance score than stronger and presumably more reliable positive patch test reactions."	Lachapelle et al ¹²
European Society of Contact Dermatitis	2015	"A patch test reaction scored as doubtful means that the morphology is not clear-cut 'irritant' or 'allergic.' This implies that further investigations may have to be performed. The patch test concentration used may be too low... may also be attributable to cross-reactivity to another substance... may also be marginally irritant... Repeat patch testing or serial dilution patch testing may be helpful in clarifying the nature of the reaction."	Johansen et al ¹³
AAAAI/ACAAI	2015	"Doubtful (?+) or weakly positive (1+) questionable or irreproducible reactions on PT can be easily misinterpreted... Use the repeated open application test (ROAT) to further evaluate a patient suspected of ACD who exhibits doubtful or negative PT responses, to confirm that the patient is reacting to that particular product or to determine clinical tolerability to new cosmetic products."	Fonacier et al ⁶
British Association of Dermatology	2017	Doubtful reaction categorized by erythema only, no infiltration. No further recommendation as to relevance.	Johnston et al ¹⁴
NACDG*	2018	"A final determination of 'allergic/positive' or 'not allergic' was determined by each investigator based on the temporal pattern (crescendo/decrecendo), patch test appearance, and known characteristics of that allergen. For example, a weak/doubtful (macular erythema) reaction to a formaldehyde-releasing agent could be determined to be an allergic/positive reaction in the setting of multiple or stronger reactions to related formaldehyde-releasing allergens."	DeKoven et al ¹⁵

*This statement was derived from the group statement of the most recent NACDG report rather than published guidelines.

ACD indicates allergic contact dermatitis; PT, patch test.

and 54.5% also had a positive reaction to an individual ingredient of the mix.¹ In 2010, Hervella-Garcés et al² found that relevance of doubtful reactions was 47.1% and relevance of weak reactions was actually less, at 44.3%. Relevance of late (day 7) doubtful reactions has been reported to be even higher (79%) on mailed follow-up surveys.³

How Subjective Are Doubtful Patch Test Reactions?

Uter et al³⁴ reported that when providers were shown a patch test image without and then with allergen information, 17 (13%) of 122 participants reclassified a correctly identified doubtful reaction

to thiuram, considered a "straightforward allergen," to + or ++ despite the obvious absence of infiltration.

DISCUSSION

In the present study, we reviewed the guidelines of multiple patch test groups, which are also those followed by most health care providers who perform patch tests. We found that some of the guidelines consider doubtful reactions as possible positive reactions, which may be relevant. Despite this, most studies (16/19 [84%]) describing the results of patch testing do not report doubtful reactions at all. Despite

a small sample size among the groups that include doubtful reactions as positive if deemed relevant, no significant increase was apparent in the reaction rates reported in these studies.

Interpretation of patch test reactions for patients who have reactions to unusual allergens can be challenging. For allergens such as those in an institution's supplemental series or a patient's home product, there is often a paucity of reports of the types and relevance of reactions, let alone enough data to adequately assess doubtful reactions.

Doubtful reactions have often been reported of patients taking immunomodulatory treatments, and it has been suggested that these should be assessed for relevance.³⁵ There is an increasing number of reports of patch testing in a growing population of patients receiving immunomodulatory medications for such conditions as inflammatory bowel disease, psoriasis, and rheumatoid arthritis, for which discontinuation would be unrealistic. Early research has focused on proving that positive patch test reactions, including strong reactions, are possible for these patients.^{36–38} In a study reporting all skin reactions to allergens of a standard series for 8 patients taking methotrexate or mycophenolate, 4 patients (50%) had at least 1 allergic reaction, and of the 24 total reactions, 11 (46%) were doubtful (macular erythema) reactions.³⁸ Until prospective studies are done with patients undergoing patch testing before and after initiation of various immunomodulatory therapies, providers will not know the true effects on the profile of patch test results. Consequently, some authors have suggested “overreading” doubtful and IR reactions to lower the threshold of a positive response, knowing that a patient is less likely to mount a strong immune response while taking these medications.³⁵

What Can Be Done to Address the Debate of Doubtful Patch Test Reactions in Academic and Everyday Clinical Settings?

Certainly, the recommendation of the NACDG of considering the patient's entire reaction profile can be helpful in ascertaining the importance of doubtful reactions. The example given by the NACDG is that of a doubtful reaction to a formaldehyde-releasing agent in the setting of stronger allergic reactions (or lack thereof) to other formaldehyde-releasing agents, and this example is highly applicable.¹⁵

Some authors suggest repeating patch testing for those allergens with doubtful reactions to reassess the reaction. Factors to consider include the observation that the stronger the patch test reaction, the more likely it is that the test is indicative of true allergic sensitization. Both relevance¹ and persistence³⁹ have been shown to increase with the strength of the patch test reaction. Other factors to be considered are that the nonreproducibility of positive patch tests decreases with the increased strength of reaction, and there is considerable right-left variation in simultaneous use tests.⁴⁰

It has been postulated that the reaction index (RI)⁴¹ and the positivity ratio (PR)⁴² may be helpful as tools that can help patch test providers understand the reaction profile of a given allergen. The formula for RI is positive reactions (+, ++, and +++ reactions) minus IR and +? reactions (doubtful reactions) divided by the totality

of all of the included reactions (+, ++, +++, IR, and +? reactions)⁴¹; the formula for the PR is the amount of + reactions divided by the total of +, ++, and +++ reactions for a given allergen.⁴² These formulas can provide valuable information about so-called problem allergens—those with many doubtful and IR reactions (RI < 0) and with a high percentage of positive reactions being weak (PR > 80%) (Table 2). In a retrospective review of the patch tests of 7635 patients to the TRUE test in Odense University Hospital for 15 years, Andersen and Andersen⁴⁴ found lower RIs⁴¹ and lower PRs⁴² compared with the original, previously cited reports by the Information Network of Departments of Dermatology. Andersen and Andersen⁴⁴ suggested that the differences highlight the subjectivity of RI and PR, such as (a) minor, unreported differences between the interpretation of doubtful and IR and the differences between doubtful and weak reactions among patch test groups; (b) differences in interpretation among providers; and (c) differences in allergen formulation. Although calculations of RI and PR come with this subjectivity,^{44,45} it is advocated that they can still allow patch test providers to better interpret borderline reactions in the clinical setting.⁴⁶

When a doubtful reaction is considered for possible relevance, follow-up testing can help clarify the clinical interpretation of the reaction. In ROAT, where substances are applied to an anatomic site daily at a lower, although cumulatively similar, dose than for traditional patch testing,^{47,48} a positive reaction usually occurs between 6 and 7 days and is more likely to be relevant to the patient in everyday life. Repeated open application test currently is recommended in multiple patch testing guidelines for the follow-up of a doubtful test.^{11–13} Nonetheless, even a ROAT does not always correlate with positive patch test reactions ($\geq 1+$)^{49,50} and lacks a standardized method for the clinical setting. In a recent survey of 67 patch test providers, 80% reported administering at least 1 or 2 patch tests per week, but only 40% reported administering 1 or 2 ROATs per week, with many (44.6%) administering only 1 or 2 ROATs per month.⁵¹

Simultaneous sodium lauryl sulfate testing also has been shown to aid in the interpretation of doubtful reactions because it provides

TABLE 2. Selected Problem Allergens—Those With Reaction Index <0 and Positivity Ratio >80%

Benzalkonium chloride
Benzylhemiformal
Methylene-bis(methyloxazolidine)
Glutaraldehyde
Iodopropynyl butylcarbamate
Amerchol L-101
Cocamidopropyl betaine
Octyl gallate
Sorbitan sesquioleate
Triethanolamine
Benzoyl peroxide
Chlorhexidine digluconate
Phenylmercuric acetate
Povidone iodine
1,3-Diphenylguanidine

Modified and reprinted with permission from Geier et al.⁴³

insight into the baseline irritability of a patient's skin at the time of testing,^{52,53} but it can cause an uncomfortable IR reaction.^{52,54} Other reported and possibly up-and-coming technologies for assessment of allergic doubtful reactions include optical coherence tomography,⁵⁵ confocal laser scanning microscopy,⁵⁶ and dermoscopy.⁵⁷

CONCLUSIONS

There are few data that examine the significance and relevance of doubtful patch test reactions. Some evidence has shown that these reactions may be common and may be of relevance to a patient's presenting problem.^{1–3,5,32} Although some guidelines suggest that these reactions should be evaluated further, reports of the results of patch testing often discount these reactions and systematically document them as negative. In epidemiologic reports and allergen profiles, we suggest that it is important to report the frequency of this reaction to adequately understand an allergen's reaction profile. Follow-up reports and comprehensive reviews can then ascertain advanced statistics, such as RI and PRs, which may prove valuable for patients taking immunomodulatory medications, as well as the “dubious” doubtful reactions. In the clinical context, we recommend that doubtful reactions be viewed with the same scrutiny as stronger allergic reactions because they may ultimately prove relevant in the location and timing of a patient's allergic contact dermatitis.

REFERENCES

- Devos SA, Constandt L, Tupker RA, et al. Relevance of positive patch-test reactions to fragrance mix. *Dermatitis* 2008;19(1):43–47.
- Hervella-Garcés M, García-Gavín J, Silvestre-Salvador JF; en representación del Grupo Español de Investigación en Dermatitis de Contacto y Alergia Cutánea (GEIDAC). The Spanish standard patch test series: 2016 update by the Spanish Contact Dermatitis and Skin Allergy Research Group (GEIDAC). *Actas Dermosifiliogr* 2016;107(7):559–566.
- Carlson S, Gipson K, Nedorost S. Relevance of doubtful (“equivocal”) late patch-test readings. *Dermatitis* 2010;21(2):102–108.
- Wilkinson DS, Fregert S, Magnusson B, et al. Terminology of contact dermatitis. *Acta Derm Venereol* 1970;50(4):287–292.
- Davis MD, Yiannias JA. Should macular erythema reactions be counted as positive allergic patch-test reactions? *Dermatitis* 2006;17(1):12–14.
- Fonacier L, Bernstein DI, Pacheco K, et al; American Academy of Allergy, Asthma & Immunology; American College of Allergy, Asthma & Immunology; Joint Council of Allergy, Asthma & Immunology. Contact dermatitis: a practice parameter-update 2015. *J Allergy Clin Immunol Pract* 2015;3(Suppl 3):S1–S39.
- Svedman C, Isaksson M, Björk J, et al. ‘Calibration’ of our patch test reading technique is necessary. *Contact Dermatitis* 2012;66(4):180–187.
- Tanno LK, Darlenski R, Sanchez-Garcia S, et al. International survey on skin patch test procedures, attitudes and interpretation. *World Allergy Organ J* 2016;9:8.
- Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs—an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013;68(6):702–712.
- Drake LA, Dorner W, Goltz RW, et al. Guidelines of care for contact dermatitis. Committee on Guidelines of Care. *J Am Acad Dermatol* 1995;32(1):109–113.
- Leitlinien der Deutschen Dermatologischen Gesellschaft; Deutschen Gesellschaft für Allergie und klinische Immunologie, Schnuch A, Aberer W, Agathos M, et al. Performing patch testing with contact allergens [in German]. *J Dtsch Dermatol Ges* 2008;6(9):770–775.
- Lachapelle JM, Maibach HI, Ring J, et al. *Patch Testing and Prick Testing: A Practical Guide Official Publication of the ICDRG*. 2nd ed. Berlin, Heidelberg: Springer Berlin Heidelberg; 2009.
- Johansen JD, Aalto-Korte K, Agner T, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing—recommendations on best practice. *Contact Dermatitis* 2015;73(4):195–221.
- Johnston GA, Exton LS, Mohd Mustapa MF, et al. British Association of Dermatologists' guidelines for the management of contact dermatitis 2017. *Br J Dermatol* 2017;176(2):317–329.
- DeKoven JG, Warshaw EM, Zug KA, et al. North American Contact Dermatitis Group patch test results: 2015–2016. *Dermatitis* 2018;29(6):297–309.
- Veverka KK, Hall MR, Yiannias JA, et al. Trends in Patch Testing With the Mayo Clinic Standard Series, 2011–2015. *Dermatitis* 2018;29(6):310–315.
- Uter W, Amario-Hita JC, Balato A, et al. European Surveillance System on Contact Allergies (ESSCA): results with the European baseline series, 2013/14. *J Eur Acad Dermatol Venereol* 2017;31(9):1516–1525.
- Yu DS, Kim HJ, Park YG, et al. Patch-test results using Korean standard series: a 5-year retrospective review. *J Dermatolog Treat* 2017;28(3):258–262.
- Liniauskiėnė K, Malinauskienė L, Blažienė A. Time trends of contact allergy to the European baseline series in Lithuania. *Contact Dermatitis* 2017;76(6):350–356.
- Diepgen TL, Ofenloch RF, Bruze M, et al. Prevalence of contact allergy in the general population in different European regions. *Br J Dermatol* 2016;174(2):319–329.
- Toholka R, Wang YS, Tate B, et al. The first Australian baseline series: recommendations for patch testing in suspected contact dermatitis. *Australas J Dermatol* 2015;56(2):107–115.
- Mahler V, Geier J, Schnuch A. Current trends in patch testing—new data from the German Contact Dermatitis Research Group (DKG) and the Information Network of Departments of Dermatology (IVDK). *J Dtsch Dermatol Ges* 2014;12(7):583–592.
- Boonchai W, Kasemsarn P. Suitability of patch test allergens for standard series in Thai patients: ten-year retrospective review of patch test results. *J Dermatol* 2013;40(1):65–67.
- Duarte IA, Tanaka GM, Suzuki NM, et al. Patch test standard series recommended by the Brazilian Contact Dermatitis Study Group during the 2006–2011 period. *An Bras Dermatol* 2013;88(6):1015–1018.
- Cheng S, Cao M, Zhang Y, et al. Time trends of contact allergy to a modified European baseline series in Beijing between 2001 and 2006. *Contact Dermatitis* 2011;65(1):22–27.
- Dou X, Zhao Y, Ni C, et al. Prevalence of contact allergy at a dermatology clinic in China from 1990–2009. *Dermatitis* 2011;22(6):324–331.
- Yin R, Huang XY, Zhou XF, et al. A retrospective study of patch tests in Chongqing, China from 2004 to 2009. *Contact Dermatitis* 2011;65(1):28–33.
- Helsing P, Gjersvik P, Holm JO, et al. Variability in patch test reactions—first report from the Norwegian Patch Test Registry. *Contact Dermatitis* 2010;62(5):309–313.
- Lam WS, Chan LY, Ho SC, et al. A retrospective study of 2585 patients patch tested with the European standard series in Hong Kong (1995–99). *Int J Dermatol* 2008;47(2):128–133.
- Lazarov A. European Standard Series patch test results from a contact dermatitis clinic in Israel during the 7-year period from 1998 to 2004. *Contact Dermatitis* 2006;55(2):73–76.
- Akyol A, Boyvat A, Peksari Y, et al. Contact sensitivity to standard series allergens in 1038 patients with contact dermatitis in Turkey. *Contact Dermatitis* 2005;52(6):333–337.
- Wentworth AB, Yiannias JA, Keeling JH, et al. Trends in patch-test results and allergen changes in the standard series: a Mayo Clinic 5-year retrospective review (January 1, 2006, to December 31, 2010). *J Am Acad Dermatol* 2014;70(2):269–275.e264.

33. Bilcha KD, Ayele A, Shibeshi D, et al. Patch testing and contact allergens in Ethiopia—results of 514 contact dermatitis patients using the European baseline series. *Contact Dermatitis* 2010;63(3):140–145.
34. Uter W, Frosch PJ, Becker D, et al. Are we biased when reading a doubtful patch test reaction to a ‘clear-cut’ allergen such as the thiuram mix? *Contact Dermatitis* 2009;60(4):234–235.
35. Lampel HP, Atwater AR. Patch testing tools of the trade: use of immunosuppressants and antihistamines during patch testing. *J Dermatol Nurs Assoc* 2016;8(3):209–211.
36. Wee JS, White JM, McFadden JP, et al. Patch testing in patients treated with systemic immunosuppression and cytokine inhibitors. *Contact Dermatitis* 2010;62(3):165–169.
37. Fowler JF Jr, Maibach HI, Zirwas M, et al. Effects of immunomodulatory agents on patch testing: expert opinion 2012. *Dermatitis* 2012;23(6):301–303.
38. Wentworth AB, Davis MD. Patch testing with the standard series when receiving immunosuppressive medications. *Dermatitis* 2014;25(4):195–200.
39. Dittmar D, Ofenloch RF, Schuttelaar MLA. Persistence of contact allergy: a retrospective analysis. *Contact Dermatitis* 2018;78(2):143–150.
40. Rietschel RL, Fowler JF, Fisher AA. *Fisher’s Contact Dermatitis*. 6th ed. Hamilton, Ontario, Canada: BC Decker; 2008:19–21.
41. Brasch J, Geier J, Henseler T. Evaluation of patch test results by use of the reaction index. An analysis of data recorded by the Information Network of Departments of Dermatology (IVDK). *Contact Dermatitis* 1995;33(6):375–380.
42. Geier J, Uter W, Lessmann H, et al. The positivity ratio—another parameter to assess the diagnostic quality of a patch test preparation. *Contact Dermatitis* 2003;48(5):280–282.
43. Geier J, Weishaar E, Lessmann H, et al. Bewertung von Epikutantestreaktionen auf “Problemallergene” mit vermehrt fraglichen oder schwach positiven Reaktionen. *Dermatol. Beruf Umwelt* 2010;58:34–38.
44. Andersen KE, Andersen F. The reaction index and positivity ratio revisited. *Contact Dermatitis* 2008;58(1):28–31.
45. Andersen KE, Andersen F. Validity of reaction index and positivity ratio? *Contact Dermatitis* 2008;58(5):320.
46. Brasch J, Geier J. How to use the reaction index and positivity ratio. *Contact Dermatitis* 2008;59(1):63–65.
47. Hannuksela M, Salo H. The repeated open application test (ROAT). *Contact Dermatitis* 1986;14(4):221–227.
48. Nakada T, Hostynek JJ, Maibach HI. Use tests: ROAT (repeated open application test)/PUT (provocative use test): an overview. *Contact Dermatitis* 2000;43(1):1–3.
49. Ackermann L, Aalto-Korte K, Alanko K, et al. Contact sensitization to methylisothiazolinone in Finland—a multicentre study. *Contact Dermatitis* 2011;64(1):49–53.
50. Isaksson M, Gruvberger B, Goncalo M, et al. Repeated open application test with methylisothiazolinone in individuals sensitive to methylchloroisothiazolinone/methylisothiazolinone. *Contact Dermatitis* 2014;70(4):244–246.
51. Brown GE, Botto N, Butler DC, et al. Clinical utilization of repeated open application test among American Contact Dermatitis Society members. *Dermatitis* 2015;26(5):224–229.
52. Löffler H, Becker D, Brasch J, et al; German Contact Dermatitis Research Group (DKG). Simultaneous sodium lauryl sulphate testing improves the diagnostic validity of allergic patch tests. Results from a prospective multicentre study of the German Contact Dermatitis Research Group (Deutsche Kontaktallergie-Gruppe, DKG). *Br J Dermatol* 2005;152(4):709–719.
53. Brasch J, Becker D, Effendy I. Reproducibility of irritant patch test reactions to sodium lauryl sulfate in a double-blind placebo-controlled randomized study using clinical scoring. Results from a study group of the German Contact Dermatitis Research Group (Deutsche Kontaktallergie-Gruppe, DKG). *Contact Dermatitis* 1999;41(3):150–155.
54. Pasche-Koo F, Hauser C. How to better understand the angry back syndrome. *Dermatology* 1992;184(4):237–240.
55. Boone MA, Jemec GB, Del Marmol V. Differentiating allergic and irritant contact dermatitis by high-definition optical coherence tomography: a pilot study. *Arch Dermatol Res* 2015;307(1):11–22.
56. Slodownik D, Levi A, Lapidot M, et al. Noninvasive in vivo confocal laser scanning microscopy is effective in differentiating allergic from nonallergic equivocal patch test reactions. *Lasers Med Sci* 2015;30(3):1081–1087.
57. Corazza M, Toni G, Musmeci D, et al. Dermoscopy of patch test reactions: study of applicability in differential diagnosis between allergic and irritant reactions. *Br J Dermatol* 2019;180(2):429–430.