

L.T. Nicholson ¹ and A. Haemel²

¹Department of Medicine, and ²Department of Dermatology, University of California San Francisco, 1701 Divisadero Street, San Francisco, CA 94115, U.S.A.

Correspondence: Anna Haemel.

E-mail: anna.haemel@ucsf.edu

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Patient recall may be of limited use in establishing the clinical relevance of positive patch test reactions (to fragrances)

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Fragrances are among the most common contact allergens. At the same time, the diagnosis of fragrance contact allergy faces some difficulties, including whether positive patch test reactions to the most important screening marker, fragrance mix (FM) I,

always indicate sensitization and specifically whether weak positive (+) reactions may often be false positives.

In this issue of the *BJD*, Bruze et al.¹ present results from the largest repeated open application test (ROAT) follow-up study ever, involving 40 patients with a previous positive patch test reaction to FM I compared with 68 controls with negative reactions to FM I, all obtained during the 2011 European Dermato-Epidemiology Network (EDEN) fragrance study.² The main objective was to validate an algorithm for the previously used categorization of EDEN study participants as having had 'fragrance allergic contact dermatitis' by combining a positive patch test result (to FM I) with patients' recall of product intolerance and avoidance.² Thereby, valid and reliable patch test outcomes had been amalgamated with relatively 'soft' self-reported data, which I criticized at the time.³ The limited usefulness of referring to such self-report, and outcomes based on it, has now been confirmed.¹

Beyond the rather special interest of (in)validating that study approach, some aspects of the study results warrant a closer look and brief comment. Firstly, persistence of sensitization to FM I was found in 2014 in 30 of the 40 of those testing positive in 2011, albeit testing FM I in ethanol-diethyl phthalate 98/2 v/v whereas originally it was tested in petrolatum.² Notwithstanding, the resulting Cohen's kappa is 0.71 [95% confidence interval (CI) 0.57–0.85], which is quite similar to a previous result of 0.81 (95% CI 0.72–0.89) observed in synchronous application.⁴ A prerequisite of such good reproducibility is a high level of standardization.⁵

Secondly, comparing the 2014 patch test result with FM I with its ROAT result, and using the latter as external criterion, sensitivity of the FM I patch test result (+ to +++) is 86.2% (95% CI 68.3–96.1%) and specificity 88.6% (95% CI 79.5–94.7%). Hence, also the validity can be regarded as very good for this patch test preparation often criticized as causing many false-positive reactions.

Thirdly, combining, as the authors did, the patch test results of 2011 and 2014 in a 'believe the positive' fashion, arriving at 44 participants allergic to FM I, 26 of 29 positive ROATs were seen in these 44.¹ This translates to a positive predictive value (PPV) of 59%. However, even if the ROAT is close to real-life elicitation, it cannot account for aggregate exposure by multiple products containing the allergen(s), susceptible body sites such as the axilla or anogenital area, or local immunological memory and thereby, the above figure is likely an underestimation of the PPV. The more so, as for the ROAT the authors did not use fragrance concentrations as in the standard FM I (i.e. 1% each), but partly much lower concentrations for the more potent allergens as indicated by industry self-regulatory standards (FM IA). The effect of this becomes apparent when comparing the synchronous patch test results with standard FM I and the 'adapted' FM IA: only 23 were positive to FM IA of the 34 positive to FM I (i.e. 68%).

Finally, in the individual diagnostic work-up of suspected fragrance contact allergy, to just test with FM I would be insufficient – a simultaneous or subsequent patch test of its single

constituents is mandatory to pin-point the specific contact allergen(s). Nevertheless, the approach of using FM I as a mixture of eight important fragrance allergens does mimic real-life exposure, which typically is not to single but to multiple fragrances.⁶ Moreover, exposure to mixtures is relevant for (experimental) sensitization and for elicitation.⁷ Hence, for the purpose of demonstrating a relationship between patch test and ROAT reactivity, use of the FM I mixture is a conceptually strong point.

Concluding with a more general interpretation of the study results, it will often be the initial patch test result and not the patient's history that provides important clues about the cause (s) of allergic contact dermatitis. Therefore, the screening baseline series should be as pertinent as possible and updated regularly.^{8,9} Once contact allergy has been diagnosed, patient recall may be a limiting factor in establishing clinical relevance of allergic reactions. Support of unreliable recollection, for example by providing photos or bags full of (cosmetic) products for scrutiny of ingredient labelling, is thus advisable. Evidently, full ingredient information (in labelling) beyond cosmetics would also be of great benefit to both doctor and patient. Illustrating the shortcomings of human memory in this special context, the study by Bruze et al.¹ provides an important argument for us dermatologists in our quest for full product information.

W. Uter 

Department of Medical Informatics, Biometry and Epidemiology, Friedrich-Alexander University Erlangen-Nürnberg, Waldstr. 4-6, D-91054 Erlangen, Germany

E-mail: wolfgang.uter@fau.de

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Are hypertrophic scars and keloids the same?

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Severe trauma or surgical manipulation frequently results in the development of scars. With a significant decrease in mortality following surgical intervention and major trauma including burns in the past two decades, the rehabilitating and social integration of patients following an injury has been the primary focus. Improving the quality of life of patients with unwanted scars, especially the hypertrophic and keloid scars that often develop following injury or surgical procedures, has been a major unmet challenge.¹ There is a growing consensus among researchers that the prolonged inflammatory and remodeling phases result in the formation of unwanted scars; however, elucidation of definitive mechanisms and markers to distinguish between different types of scars has been difficult.² Differentiation and characterization of the scars have been limited to only clinical observation, as there is a dearth of immunological histological profiling to distinguish between keloids, hypertrophic scars and immature scars. Histological factors that have been used to make this distinction include keloidal collagen and α -smooth muscle actin (SMA).³

Although there are significant numbers of studies^{4,5} and reviews⁵ that have looked at the physiological and histological differences between normal skin, keloids and hypertrophic scars, there are almost no studies performed on immature scars. This issue of the *BJD* features an article by Limandjaja et al. that addresses this void.⁶ The study is novel in that the authors reported not only keloid, hypertrophic and normal skin, but also young immature scars, normal skin directly surrounding the keloids, and normal skin adjacent to immature scars. This wide inclusion of tissue biopsies provides a dynamic spectrum of changes occurring during the scar formation pathology.

One of the main findings of the study was that although the authors could not distinctly differentiate between keloids and hypertrophic scars based on the immunological staining, rather gradient differences were observed in the CD34⁺ α -SMA⁺ p16⁺ scar phenotype between the two types of scars