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The value of ongoing surveillance on the prevalence of contact sensitization

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Linked Article: Uter *et al.* *Br J Dermatol* 2020; **183**:857–865.

In this issue of the *BJD*, Uter *et al.* describe the results of an ongoing surveillance study on the prevalence of contact sensitization in the population of Germany, Austria and Switzerland.[1] It is, as the authors rightly comment, not based on patch testing samples of the general population, but 'aimed testing' in patients visiting the departments that are contributing to the database. Because reading a patch test result is prone to subjectivity and has a degree of interobserver and interdepartmental variability, it is reassuring to note that the participating centres meet regularly to harmonize their procedures, although it is not clear whether random external monitoring visits are being performed.[2] It is still being debated whether patch test data from clinics, obtained by 'aimed testing', are indicative of what is happening in the general population. A few studies seem to confirm that, at least in a number of European countries, it is indicative.[3] It is important to realize that the large dataset presented by Uter *et al.* is limited to the European baseline series. This series is supposed to be fairly representative, but a word of caution is needed because the hair dye ingredient *para*-phenylenediamine is no longer routinely patch tested in Germany.

Large datasets allow researchers to show time trends. Indeed, Uter *et al.* show time trends in positive reactions to the preservatives methylisothiazolinone (MI) and methylchloroisothiazolinone (MCI)/MI, which is a long-term indicator for MI allergy. The high prevalence of MI contact allergy, which had its peak around 2013–2014 in Europe, was a major trigger to ban of the use of MI in leave-on cosmetic products and restrict the maximum permissible level to 15 p.p.m. in rinse-off cosmetics.[4,5] The current publication by Uter *et al.* shows the rise and fall of contact allergy to MI, which demonstrates the success of the preventive measures that were implemented.

The data presented by Uter *et al.* on sensitization to the fragrances support the value of ongoing surveillance, because fragrance-induced contact allergy is still considered to be of high concern. Industry is more and more relying on nonanimal, *in vitro* tests to assess the potency of sensitizers that are present in marketed consumer products, to be used in a quantitative risk assessment (QRA).[6] This is promising but also shows the importance of collecting and monitoring well-performed patch test data as a kind of feedback loop to the more 'predictive' QRA. Such a well-monitored feedback loop is currently being implemented by the Extended Fragrance Ingredients Surveillance Study, to monitor the frequency of contact allergy to a defined group of existing ingredients and also to new fragrance ingredients, initiated by the International Dialogue for the Evaluation of Allergens project (IDEA; https://www.ideaproject.info).

Together, large datasets such as that presented by Uter *et al.* allow researchers to spot discrepancies and important time trends, which trigger us to regulate exposure to substances, for example by cosmetics regulation.

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Reliability and validity of the Vitiligo Signs of Activity Score

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Signs of active progression of vitiligo are important to recognize in order advise patients on prognosis and to offer appropriate management. Clinical signs such as confetti-like depigmentation, poorly defined borders and Koebner phenomenon have previously been suggested to predict disease activity.[1] Measuring the cessation of spread of vitiligo is also of great importance to patients and clinicians and should therefore be reported in future trials if relevant.[2]

In this issue of the BJD, van Geel *et al.* report on a novel tool, the Vitiligo Signs of Activity Score (VSAS).[3] This tool aims to quantify clinical signs of vitiligo activity in a standardized way for future use in clinical practice and trials. In their study, 247 ultraviolet pictures from 23 patients with vitiligo were rated by seven vitiligo experts within an interval of approximately 2 months. The authors chose three proposed signs of vitiligo activity: confetti-like depigmentation, Koebner phenomenon and hypochromic areas, which were assessed on 15 predefined body areas. The authors reported on reliability (degree of agreement between two or more raters), validity (the extent to which the score measures what it is supposed to measure) and feasibility (practicality of the score such as completion time). The authors anticipated a positive correlation of VSAS with a global disease activity score [Physician Global Assessment (PGA), using a 5-point scale]. Results showed that inter-rater agreement for grading the severity of each sign was very good for confetti-like depigmentation [intraclass correlation coefficient (ICC) of 0·83; 95% confidence interval (CI) 0·71–0·92] and fair for Koebner phenomenon (ICC 0·56; 95% CI 0·35–0·76) and hypochromic areas (ICC 0·51; 95% CI 0·31–0·71). A strong positive correlation (median r = 0·75) was found between median VSAS and the PGA. The time for VSAS completion ranged from a few seconds to several minutes.

The findings of this small, preliminary study suggested that VSAS showed good reliability, fair validity and feasibility in quantifying three possible markers of vitiligo disease activity signs (confetti-like depigmentation, Koebner phenomenon and hypochromic areas). However, important questions remain regarding the validity of the VSAS and its utility in clinical practice or future trials. Responsiveness of the VSAS to change (the ability of the score to change over a prespecified time frame) and stratification of the score and its translation into meaningful categories (e.g. mild to very severe) is yet to be determined. The reference standard for assessing dynamic disease 'activity' in this study was a static assessment by a single dermatologist, who was probably already aware of the purported clinical indicators of vitiligo activity. In order to find out how well this instrument predicts vitiligo disease activity, a cohort study is needed that measures *actual* disease progression as the reference standard. The responsiveness of VSAS to change should also be defined along with a deeper understanding of the interpretability of the change in VSAS score to ensure that it is meaningful to both patients and clinicians.

The authors' choice of the three clinical signs warrants further scrutiny as the same researcher group previously reported that only Koebner phenomenon was strongly associated with disease activity and that more data are needed to confirm that poorly defined borders and confetti lesions are potential markers of vitiligo activity.[4] It is also important to estimate how often these signs occur in a typical cohort of patients with vitiligo. If, for example, confetti-like hypopigmentation is confirmed to be associated with vitiligo activity but occurs only infrequently, then the VSAS will not be relevant to the majority of patients with vitiligo.

Despite these shortcomings, this work on the VSAS was a promising start that reduced some uncertainties about the performance of the tool which now needs to be followed up in a cohort study that evaluates the dynamic process of vitiligo over time, and to see what the predictive values of these signs are in what proportion of patients with vitiligo.

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