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**Repigmentation in vitiligo: position paper of the Vitiligo Global Issues Consensus Conference (VGICC)**

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**SUMMARY**

The Vitiligo Global Issues Consensus Conference (VGICC), through an international e-Delphi consensus, concluded that "repigmentation" and "maintenance of gained repigmentation" are essential core outcome measures in future vitiligo trials. This VGICC position paper addresses these core topics in two sections and includes an atlas depicting vitiligo repigmentation patterns and color match. The first section delineates mechanisms and characteristics of vitiligo repigmentation and the second summarizes the outcomes of international meeting discussions and two e-surveys on vitiligo repigmentation, which had been carried out over three years. Treatment is defined as successful if repigmentation exceeds 80% and at least 80% of the gained repigmentation is maintained for over 6 months. No agreement was found on the best outcome measure for assessing target or global repigmentation, therefore highlighting the limitations of e-surveys in addressing clinical measurements. Until there is a clear consensus, existing tools should be selected according to the specific needs of each study. A workshop will be conducted to address the remaining issues so as to achieve a consensus.

**SIGNIFICANCE**

There is a need to clearly describe and define the various aspects of vitiligo repigmentation. The discussions at international meetings and e-surveys have sought to address both the issues of repigmentation and the maintenance of gained repigmentation.

**KEYWORDS:** Repigmentation; vitiligo; pigment; repigmentation pattern; outcome measure

**RUNNING TITLE:** Repigmentation in vitiligo: VGICC position paper

## INTRODUCTION

The Vitiligo Global Issues Consensus Conference (VGICC) is an international initiative that started in 2010 after informal discussions at dermatology and pigment cell meetings in Europe, Asia and United States of America. After preparatory meetings, the VGICC met twice in 2011, with a first conference hosted by the Korean Vitiligo Society during the Seoul World Congress of Dermatology (WCD), and the second during the International Pigment Cell Conference (IPCC) in Bordeaux. The first topic of the VGICC was nomenclature and related issues, and the consensus paper published in PCMR in 2012 (Ezzedine et al., 2012) was a landmark for international vitiligo cooperation. Since 2012, the priority of the VGICC has been to address outcome measures, as novel molecules and devices will likely increase the development of academic and industrial vitiligo research. We must be prepared with common validated international nomenclature and classifications that can be confidently used in this setting. Over the past three years, questionnaire surveys were administered at international meetings utilizing a methodology developed by dermato-epidemiologists within a framework developed by rheumatologists (OMERACT-Outcome Measures in Rheumatoid Arthritis Clinical Trials- , COMET- Core Outcome Measures in Effectiveness Trials-). Physicians, patients, journal editors, and health agency representatives had the opportunity to complete the surveys at several international conferences, including the following: American Academy of Dermatology (AAD) (Miami 2013, Denver 2014), European Academy of Dermatology and Venereology (EADV) (Istanbul 2013, Amsterdam 2014), IPCC (Singapore 2014) and WCD (Vancouver 2015). Patients were from the established support groups of the various regional areas (Europe, continental Asia, Japan-Taiwan, Middle East, Pacific, North and South America) and were contacted to participate by the regional coordinators. Recently, a report of the consensus reached on core outcome domains for the assessment of vitiligo was released, which concluded that "repigmentation", "maintenance of gained repigmentation" and "side effects and harms" of treatment are outcome measures that should be measured in all future vitiligo trials (Eleftheriadou et al., 2015).

Now that these domains have been selected, tools are needed for practical measurements. The first priority of the VGICC is to define future directions for the assessment of repigmentation and the maintenance of gained repigmentation as these were deemed the most important by stakeholders and panellists. This position paper summarizes the current status of this project over the past three years and is divided into 2 sections. The first section reviews various important aspects of vitiligo repigmentation and the second section summarizes the outcome of the 2 e-surveys and the meeting discussions.

Section I

**Defining repigmentation in vitiligo**

In the latest update of the Cochrane review on vitiligo interventions in 2015, all 96 studies reviewed assessed repigmentation (Whitton et al, 2015). In 2012, a systematic review of 54 eligible trials also showed that repigmentation was the most frequently reported outcome in 96% of trials and the authors proposed that future vitiligo trials should report repigmentation, among other outcome measures (Eleftheriadou et al., 2012). However, defining repigmentation in vitiligo is not straightforward. Major issues in the assessment of repigmentation, namely biology and mechanisms of repigmentation, patterns of repigmentation, and color match, are reviewed below.

- **Biology and mechanisms of repigmentation**

Repigmentation in vitiligo is known to occur after treatment or spontaneously in a few cases (Alikhan et al., 2011). Known sources of melanocytes for repigmentation include the hair follicle unit (Ortonne et al., 1979; Cui et al., 1991; Grichnik et al., 1996; Falabella, 2009; Goldstein et al., 2015), the depigmented epidermis (Tobin et al., 2000; Zabierowski et al., 2011) and the edge of vitiligo lesions (Falabella, 2009).

In a landmark study published in 1979, Ortonne et al concluded that melanocytes repigmenting vitiliginous skin under the influence of oral photochemotherapy are derived from a melanocytic reservoir in the hair follicle (Ortonne et al., 1979). Cui et al later reported that inactive melanocytes in the outer root sheath mature as they reach the nearby epidermis (Cui et al., 1991). In 1996, Grichnik et al found that immature dendritic, tyrosinase negative and c-kit positive pigment cells mainly concentrated around the follicular ostium, rete pegs and outer root sheath were also a source of epidermal repigmentation (Grichnik et al., 1996). Further research into stem cells has shown that the primary melanocyte germ cell is present in the hair follicle bulge region (reviewed in Falabella, 2009), while a possible secondary melanocyte source composed of c-kit+ melanocytes is found in the infundibulum and interfollicular epidermis, as is evident in UV-treated vitiligo lesions (Goldstein et al., 2015).

Other studies have shown that the depigmented epidermis may still contain melanocytes (Tobin et al., 2000) and these can recover their functionality both *in vivo* and *in vitro*. Moreover, non-melanogenic melanocytes exist in several adnexal exocrine compartments of the skin, including sebaceous glands (Ito et al., 1976; Jang et al., 2014). Dermal stem cells from glabrous skin also exist and may serve as a self-renewing source of extrafollicular epidermal melanocytes (Li et al., 2010). The role of Schwann cells as a reservoir in humans is debated (Adameyko, et al., 2009). Sweat glands also harbor melanocyte stem cells (Glover et al., 2015) and it is these sources that likely contribute to the

clinically diffuse pattern of repigmentation that is observed in some vitiligo lesions. However, the diffuse pattern of repigmentation still remains questioned among experts.

The exact molecular and cellular mechanisms underlying the recruitment, activation, maturation and proliferation of melanocyte precursors, culminating in vitiligo repigmentation, still remain to be fully elucidated. Figure 1 summarizes the possible mechanisms occurring in repigmentation of vitiligo skin. These serve two main purposes, to achieve adequate melanocyte stimulation and to enhance the melanocyte environment for the events leading up to repigmentation. Direct migration of follicular melanocyte stem cells to the epidermis has been demonstrated after UVB irradiation (Chou et al., 2013). Migration was dependent on presence of the melanocortin-1 receptor in melanocytes, which binds melanocortins such as α-melanocyte-stimulating hormone (α-MSH) with high affinity. In UV-induced repigmentation of vitiligo, Wnt7a via β–catenin activation, also triggers differentiation of melanocyte stem cells into melanoblasts in hair follicles, ultimately leading to their proliferation and initiation of melanogenesis (Yamada et al., 2013). Besides melanocytes, other resident cutaneous cells also play important roles in modulating epidermal pigmentation. Keratinocytes can modulate the biological behavior of neighboring melanocytes through their various growth factors and mitogens including α-MSH, stem cell factor (SCF/KIT-ligand), basic fibroblast growth factor (bFGF), endothelins and nerve growth factor (Hsin-Su, et al., 2010; Imokawa, 2004). It is likely that these factors act in a synergistic manner during repigmentation in vitiligo. For example, α-MSH increases expression of the receptors for SCF and hepatocyte growth factor (HGF), (Wu et al., 2000; Beuret et al., 2007) both of which are important melanocyte growth and migration factors. Moreover, α-MSH also stimulates Wnt7/β-catenin signaling (Bellei et al., 2011). Dermal fibroblasts are also believed to influence skin pigmentation (reviewed in Yaar, 2013), albeit to a lesser degree compared with keratinocytes, via secretion of factors such as HGF, SCF and neuregulin-1 (Choi et al., 2010), although their negative effects on epidermal pigmentation have also been reported (Cario-André et al., 2006). A recent transcriptional study showed that Wnt signaling is impaired in lesional and non-lesional skin of patients with vitiligo. The authors demonstrated that oxidative stress in melanocytes and keratinocytes decreases Wnt signaling and thus might contribute to inhibit melanocyte regeneration. By stimulating the Wnt pathway using Wnt agonists or GSK3b antagonists, they managed to induce melanoblast differentiation in an *ex vivo* model using vitiligo patient skin (Regazzetti et al., 2015). Interestingly, the Wnt pathway is physiologically inhibited in palms and soles due to the secretion of DKK1 by fibroblasts (Yamaguchi et al., 2007; Yamaguchi et al., 2008). This might explain why repigmentation is so difficult to achieve in these locations. Taken together, these data emphasize the key role of Wnt signaling for melanoblast differentiation and suggest that activating the Wnt pathway could be a powerful therapeutic strategy for repigmenting vitiligo lesions.

Several studies have described possible additional mechanisms by which repigmentation occurs after surgical grafting of vitiligo. Firstly, the injury and healing process due to the grafts stimulates the dissociation of melanocytes from the basal layer, their proliferation, migration and repositioning in the basal layer, essentially the normal physiologic process for melanocyte homeostasis. This favorable environment for melanocyte stimulation is created by the promotion of pro-melanogenic factors such as HGF, bFGF, keratinocyte growth factor (Cardinali et al., 2005; Kovacs et al., 2010; Muller et al., 2012). Another postulated mechanism involves alterations in the dermal-epidermal junction (DEJ) and the increase in heparanase post-grafting (Kovacs et al., 2015). Heparanase-mediated reduction of heparan sulphate at the DEJ is believed to increase the transfer of pro-melanogenic heparin-binding growth factors such as FGF and hepatocyte growth factor from the dermis to melanocytes (Kovacs et al., 2015). Thirdly, matrix metalloproteinases (MMPs) such as MMP-2, which are upregulated in wound healing, also contribute to melanoblast migration [Lei et al., 2002]. Lastly, the downregulation of adhesion molecule E-cadherin, which leads to enlargement of epidermal intercellular spaces (Gauthier et al., 2013), occurs during wound healing (Kuwahara et al., 2001). This is believed to facilitate melanocyte migration and it has been demonstrated in repigmented skin post punch grafting (Kovacs et al., 2015).

- **Vitiligo repigmentation characteristics**

**(a) Vitiligo repigmentation patterns**

Patterns of repigmentation so far studied are mainly those seen with medical therapy, especially phototherapy. Surgical methods have at least transiently different repigmentation patterns: circular or pseudopod-like outgrowths with minigrafts (Falabella, 1986), diffuse (sometimes blotchy) repigmentation with non-cultured autologous epidermal suspensions, non-cultured extracted hair follicle outer root sheath cell suspensions or blister grafts (Budania et al., 2012; Kumar et al., 2014; Singh et al., 2013). Unfortunately, there is a lack of controlled studies assessing vitiligo repigmentation patterns.

Considering articles studying specifically repigmentation, the largest study published to date analyzed 352 vitiliginous patches in 125 Indian patients who received various treatment modalities. Four patterns of repigmentation described were marginal, perifollicular, diffuse and combined (Parsad et al., 2004). The most commonly reported pattern of repigmentation was perifollicular (55%, n=194), followed by diffuse (28%, n=98), combined (13%, n=45) and marginal (4%, n=15). In the same study, when gained repigmentation was assessed 6 months after cessation of active treatment, marginal repigmentation was most stable (93%), followed by perifollicular (92%), combined (84%) and diffuse (79%) types. The authors also analyzed the speed of repigmentation and reported faster repigmentation when the initial noted pattern was diffuse, as compared to perifollicular

repigmentation. Two smaller studies from Asia have confirmed the repigmentation patterns observed in Indian vitiligo patients (Kim et al., 2005; Yang et al., 2010). In a recent retrospective study, the repigmentation patterns of 109 European pediatric vitiligo patients were analyzed, thus limiting confounding factors such as senescence of melanocyte precursors or presence of concomitant dermatological conditions that could affect cutaneous melanocytes (Gan et al, 2016a). In this cohort that received various treatment modalities, the combined repigmentation pattern was the most commonly observed pattern (62%, n=106), followed by diffuse (25%, n=43), marginal (6%, n=11), perifollicular (5%, n=9) and lastly, a proposed new pattern, medium spotted repigmentation (2%, n=3). Medium spotted repigmentation describes a distinct pattern of repigmentation that has been observed to occur in glabrous or minimal hair-bearing sites, such as palms, soles, ankles, and volar wrists. In these cases, the repigmentation begins as a larger spot that is not centered on a hair follicle, in contrast to perifollicular repigmentation, where pigmentation starts around the follicular ostia (Parsad et al., 2004). Representative photographs of the various repigmentation patterns are provided in Appendix S1 (Figures S1-S9).

Apart from age group affecting repigmentation patterns, the type of medical treatment may have a role in influencing the pattern of repigmentation. Parsad et al reported that treatment with psoralens predominantly leads to a perifollicular pattern of repigmentation, whereas treatment with corticosteroids (topical or systemic) tends to exhibit a diffuse pattern (Parsad et al., 2004). In addition, marginal repigmentation has been noted to occur in non-hair bearing areas after phototherapy (unpublished data communicated by S. Thng). In pediatric vitiligo, Gan et al found that the diffuse pattern of repigmentation was more common in patients treated with topical calcineurin inhibitors as compared to topical corticosteroids (Gan et al., 2016a). In another study exploring the use of alpha-MSH analogue as an adjunct to NBUVB phototherapy in Asian adults (unpublished data communicated by S. Thng), the repigmentation pattern was noted to be mainly perifollicular and medium spotted in all patients, with minimal evidence of marginal or diffuse pigmentation. This observation suggests that α-MSH is capable of stimulating melanocytic stem cells in both the follicular and extrafollicular stem cell compartments. However, larger scale studies are needed to further delineate the relationship between the type of treatment and repigmentation patterns.

**(b) Color match**

Currently, a limited number of studies have analyzed the degree of color mismatch post-treatment (Olsson and Juhlin, 2002; Gupta et al., 2002; van Geel et al., 2010). Studies evaluating color match usually employed subjective methods such as digital photography evaluation. An objective method of measurement, such as colorimetry, needs to be further developed and validated. A study comparing psoralen-ultraviolet A (PUVA) to NBUVB by Yones et al. (Yones et al., 2007) found that color match was better with NBUVB, even in patients with darker skin phototypes (Sami et al., 2007).

The timing of color match assessment needs consensus for interventional studies. Hyperpigmentation occurs initially in all types of vitiligo surgery. However, the ultrathin epidermal sheet method of vitiligo surgery most often resulted in a slight hyperpigmentation compared to the basal layer cell suspension method where hyperpigmentation was the least common (Olsson and Juhlin, 2002). Overall, a good color match occurs usually within a year after surgery (Falabella, 1986, Suvanprakorn et al., 1985; Skouge et al., 1992; Löntz et al., 1994; Olsson and Juhlin, 2002). In Appendix S1, there are photographs of good color match and of color mismatch with hyperpigmentation.

**Measuring repigmentation**

To date, there is no standardized, universally adopted method to measure the degree of de-/repigmentation of vitiligo (Alghamdi et al., 2012). Various methods of vitiligo assessment have been described in the literature, which can be divided into patient-reported outcomes, clinician-reported outcomes and observer-reported outcomes (Vrijman et al., 2012).

In deciding which tool is best for the assessment of repigmentation, it is important to consider that distinct tools are required for assessing global repigmentation compared to the repigmentation of target lesions. For example, assessment of target lesion repigmentation provides useful information in guiding physicians who are treating vitiligo with topical or surgical treatments, whereas a global repigmentation assessment would be more relevant in a patient who is undergoing systemic therapy such as phototherapy, systemic corticosteroids or immunosuppressants.

Patient-reported outcomes including the Vitiligo Life Quality Index (VLQI) (Sęnol et al., 2013), Vitiligo Impact Scale-22 (VIS-22) (Gupta et al., 2014), and VitiQoL (Lilly et al., 2013) do not measure repigmentation, but focus on the quality of life of patients with vitiligo. However, a newer tool, The Vitiligo Noticeability Scale (VNS), distinguishes itself by indirectly measuring repigmentation through the assessment of how 'noticeable' the vitiligo patches are after treatment (Batchelor et al., 2016). This tool, based on digitally simulated lesions, requires further "real life" validation with larger studies. The SAVASI (Komen et al., 2015a) and The Vitiligo Impact Patient scale (VIPs) (Salzes et al., 2016) have been recently introduced with the latter distinguishing between lighter and darker skin phototypes. Another more recently developed and validated patient-oriented evaluation method, the Self-assessment Vitiligo Extent Score (SA-VES), has demonstrated its usefulness and reliability as a tool for patient assessment of vitiligo extent (van Geel et al., in press).

The two most commonly utilized clinician-reported outcomes are the Vitiligo Area Scoring Index (VASI) (Hamzavi et al., 2004) and the Vitiligo European Task Force assessment (VETF) (Taïeb et al., 2007). In the VASI, the body is divided into 5 separate and mutually exclusive regions and at each

assessment, the percentage extent of residual depigmentation within each region is estimated and included in the VASI calculation (Hamzavi et al., 2004). In the VETF assessment, the extent, staging and spreading of lesions are evaluated. The palm (including digits) method is used to represent 1% of the body surface area. Staging is assessed with a Wood's lamp and is based on cutaneous and hair pigmentation of the largest macule in each body region (3 regions), except for hands and feet, which are assessed separately. The spreading score categorizes the presence of ongoing subclinical de-/ repigmentation by comparing natural light and Wood's lamp visualizations (Taïeb et al., 2007). Vitiligo repigmentation is therefore inherently accounted for in these methods. However, a truly accurate reflection of repigmentation, which indicates treatment response, requires a large enough smallest detectable change (SDC) that picks up clinically meaningful repigmentation. A recent analysis of these 2 instruments has cautioned users when interpreting score changes in individual patients because of relatively large SDC values that may result in repigmentation not being reflected by a change in score (Komen et al., 2015b). The recently proposed Vitiligo Extent Score (VES) is a new intuitive instrument with possibility to show vitiligo extent at a glance, corresponding to clinically relevant categories of global severity (van Geel et al., 2016).

Observer-reported outcomes consist of more objective methods of assessment. One of the earliest reported methods was the Digital Image Analysis System (DIAS), which performs surface measurement of vitiligo lesions (van Geel et al., 2004). The computerized digital imaging system (C-DIAS) is a newer technique for objective assessment of repigmentation, where the mathematical tools of principal component analysis and independent component analysis are used to convert 3 different spectral bands (red, green and blue) in a digital skin image into an image that represents skin areas based on melanin and hemoglobin composition (Shamsudin et al., 2015; Ahmad Fadzil et al., 2009; Nugroho et al., 2007). Recent publications on the objective measurement of vitiligo have included an automated digital image analysis system that is able to transform and align identified lesions from follow-up images with those in the initial image. This allows the percentage change in area over time, or "automated fill factor", which represents the percentage of repigmentation to be determined (Sheth et al., 2015). The emerging technique of 3D-imaging and analysis to quantify the affected body surface area of subjects with vitiligo has also been recently described (Kohli et al., 2015). Table 1 summarizes the various instruments, their inter- and intra-rater reliability and feasibility of use in trials and in clinical practice.

Non-invasive methods of assessment such as reflectance confocal microscopy are gaining recognition as possible techniques that can be used to provide information on vitiligo repigmentation. In the recovery phase of vitiligo, dendritic and highly refractile melanocytes have been reported. Three kinds of repigmentation patterns have also been elucidated on confocal microscopy, namely marginal,

where dendritic and highly refractile melanocytes are seen moving from adjacent normal-appearing area to the lesional area; perifollicular, where the melanocytes are seen surrounding the hair follicle, and lastly diffuse, where the melanocytes are evenly distributed in the lesional area (Lai and Xu, 2011).

Prediction tools for vitiligo repigmentation have also been explored. Benzekri et al. conducted a prospective observational study to develop and validate a simple vitiligo Potential Repigmentation Index (PRI) (Benzekri et al., 2013). The PRI takes into account both the total number of lesions and the individual capacity of each lesion to repigment. The latter is derived from scoring lesions into 4 clinical types of vitiligo – A, B, C and D, which presumably corresponds to the remaining follicular and epidermal reservoirs of melanocytes and precursors.

**Defining "Maintenance of gained repigmentation"**
After achieving treatment success with repigmentation in vitiligo, the ability to maintain the newly gained pigment is essential. This is important from both the physician's and patient's perspectives because persistence of repigmentation precludes the need for repeated treatments and boosts the patient's morale, quality of life and perception of the effectiveness of treatment.

Currently, a unified definition of the "maintenance of gained repigmentation" is lacking. Consensus needs to be achieved on what constitutes an ideal percentage of repigmentation compared to baseline, the duration of persistence (short-term, mid-term, long-term), the treatment status of the patient during the time of maintained repigmentation and the threshold of depigmentation allowed before a lesion is deemed to have lost its gained repigmentation. The treatment status of the patient is important because some patients may be placed on maintenance treatment, whereas others may discontinue all therapies.

The first study assessing the permanency of repigmentation was reported in 1971, where 20 out of 21 psoralen-treated vitiligo patients maintained their pigmentation 8 to 14 years after finishing psoralen without further treatment (Kennedy JA Jr, 1971). Other studies on phototherapy intervention in vitiligo have subsequently been published, evaluating various follow-up periods that range from 12 to 66 months (Westerhof and Nieuweboer-Krobotova, 1997; Kwok et al., 2002; Sitek et al., 2007). A 10-year retrospective analysis of the use of PUVA in the treatment of vitiligo showed that patients who retained their pigmentation after 2 years appeared to have a better chance of permanent remission (Kwok et al., 2002). The longer-term studies tend to be in patients who had undergone vitiligo surgery. These studies encompass a range of surgical techniques, such as transplant of cultured melanocyte suspension, punch grafting, autologous epidermal grafting, and non-cultured cellular grafting. Follow-up periods varied, with a maximum of 14 years in a study published by Lu et al in 2014 (Chen et al., 2004; Mulekar, 2005; Fongers et al., 2009; Mulekar et al., 2010; van Geel et al.,

2010; Lu et al., 2014; Gan et al., 2016b). It is however difficult to compare these studies, as they were not standardized in many ways.

Patients with segmental vitiligo tend to retain their repigmentation more than patients with vitiligo vulgaris. In a study of 177 patients with stable vitiligo treated with cellular grafting, about 11% of patients had loss of repigmentation at the 60-month follow up. All of these patients had non-segmental vitiligo with a subsequent flare of active disease (Gan et al., 2016b).

Some of the obstacles that clinicians may face when trying to conduct long-term studies for maintenance of gained repigmentation include a gradual loss to follow-up and the current lack of clear definitions of persistent repigmentation. Therefore, a consensus needs to be achieved so that future studies can have well-defined objectives with easily comparable and interpretable results.

**Section II**

**VGICC repigmentation e-surveys and discussions (2013-15)**

This section summarizes the points discussed at international meetings following the administration of 2 e-surveys. Among the essential outcome domains identified by the first e-delphi consensus, repigmentation was elected to be the first domain for which tools of measurements should be defined. The following 5 questions were proposed to 45 international experts using a first e-survey, which received a 100% response rate:

I- How would you define "repigmentation" in vitiligo?

II- What is the set of minimal tools for the assessment of "repigmentation"?

III- What are the relevant endpoints for extent and speed of repigmentation in randomized controlled trials (RCTs)?

IV- What should be the definition of "maintenance of gained repigmentation"?

V- What are the qualitative and quantitative methods to assess "maintenance of gained repigmentation"?

A further face-to-face meeting was conducted during the 2014 AAD conference in Denver, Colorado, during which the results of the e-survey were presented and discussed.

**Repigmentation patterns**: The proposed items for patterns of repigmentation (follicular, marginal, central non-follicular) were commented upon in terms of pathophysiology (melanocyte migration) and prognosis i.e. durability/maintenance of gained repigmentation, with the need to make prospective correlations. The proposal of a "combined pattern" was agreed upon. There was no complete consensus on the existence of the diffuse repigmentation pattern, with several panellists emphasizing the need to meticulously examine any area of diffuse repigmentation with a Wood's lamp to exclude a

perifollicular pattern. The need for an illustrative atlas with photographs before and after treatment to illustrate the defined repigmentation patterns and the grading of color match was also highlighted in the discussion (see Appendix S1). The issue of skin phototype influencing the repigmentation pattern was also discussed and it was commented that in patients with darker skin phototypes, the efficiency of repigmentation is increased.

**Set of minimal tools for the assessment of repigmentation:** Photography, including ring light photography was deemed to be the most important (40/45) mode of assessment as compared to digital analysis, Wood's lamp, UV photographs, and chromametry (26, 22, 20 and 13 out of 45 answers respectively). In order to obtain an appropriate analysis, the need to distinguish systemic from local intervention was highlighted. **For target lesion assessment** there was an agreement on a distinction between "acceptable/minimal" and "optimal" sets of tools, which would depend on feasibility and financial considerations. Photography was deemed the major tool for minimal assessment of target lesions. Ring flash, as recommended by the Japanese group, was used routinely by only 1/10 of participants. The need for UV light photography was acknowledged for light skin phototypes. Suggestions such as the replacement of costly UV light devices by a digital switch to blue channel to increase contrast and the measurement of lesion size with the incorporation of a ruler in the camera need to be explored. Chromametry should ideally be included in the set for colour match evaluation. **For global assessment**, the VASI score needs to be considered given its validation in clinical trials. The VETF score is more useful for baseline evaluation as it was not designed to be sensitive to rapid changes. A minimum body surface area (BSA) involved for the assessment of a systemic intervention was discussed, which can be compared to the minimum PASI score of 10-12 for psoriasis. However, a median of 2% BSA is found in most European academic centres for newly referred vitiligo patients.

**Relevant endpoints for assessing extent and speed of repigmentation in the context of randomized trials:** This point lacked consensus based on e-survey. The distinction between acral and non-acral lesions was debated, with acral referring to the hands and feet. The exclusion of acral lesions from major evaluation endpoints was proposed as these areas are generally resistant to treatment. Based on the existing data on UVB treatment, 40-50% repigmentation is expected after six months. The general agreement was to propose 50% repigmentation at 6 months as a threshold for treatment success, with a debate on continuous vs non-continuous binary variables in defining success. Grading responses into complete versus partial response was also considered. In any case, the type of intervention considered and the association or not with phototherapy may change the expected threshold for treatment success.

Another general issue discussed was the **need to include both patients with stable and active/progressing disease in studies using systemic interventions**. For the latter group, a cessation

of depigmentation after three months of systemic intervention could be an acceptable endpoint. The need of biomarkers either in skin or blood was emphasized at this early evaluation point of 3 months. Non-invasive parameters, such as clinical patterns and confocal microscopy to detect infiltrates would also be worth considering.

**Definition of "maintenance of gained repigmentation" in vitiligo**: Based on the results of the survey, the majority of experts defined success as up to a 20% loss of gained repigmentation over one year (from 0 to 10-20%). However, considering the cost of long-term observation in RCTs, the majority was in favour of limiting the period of observation to 6 months, while maintaining the same definition of success (up to 20% loss of gained repigmentation). The maintenance of gained repigmentation with versus without treatment was also discussed, because the concept of maintenance treatment for a chronic disease like vitiligo is gaining acceptance, and may become a standard of care. The concept of time to relapse after cessation of treatment needs to be included in clinical trials. Therefore, a distinction between loss of gained repigmentation and a new flare (new spots, enlargement of old lesions) is necessary. For the assessment of "maintenance of gained repigmentation", the panellists made the same recommendations as for the assessment of initial repigmentation. The addition of patient-related outcome measures should be considered. The relationships, if any, between the location of relapses, repigmentation patterns and the maintenance of gained repigmentation should also be analyzed.

**Scales to measure repigmentation in clinical trials, and choice of time points:** A second e-survey was conducted before the IPCC 2014, involving 94 panellists (The e-delphi reached a response rate of 94% with 94 participants from 25 countries including 61 dermatologists , 21 patients and/ or caregivers, 5 journal editors and 7 researchers, see list in Appendix S2). After a large discussion (in Singapore, IPCC 2014) on the results of this second e-survey, no agreement was found on the best outcome measure to assess target or global repigmentation. As reviewed above, recently published papers have highlighted the limitations of the VASI and VETF scales for smallest detectable change (Lim et al., 2015; Komen et al., 2015b).

For target lesion repigmentation, the percentage categories used in VASI: 0-24%; 25-49%; 50-74%; 75-90%; 91-100% scored best (49%) as compared to quartiles and continuous scoring from 0-100%. For color match, the categories "lighter, same, darker" were preferred by the majority (83%). With respect to time points in assessing color match in clinical trials, the majority of panellists (58%) chose 3 months after completion of treatment. For measuring successful repigmentation in clinical trials, 40% of panellists chose 6 months of intervention but 21% did not reply because the answer was felt to be too dependent on the type of treatment.

**Definition of successful percentage of repigmentation**: This exercise was performed using a computerized image, with 67% of panellists defining success as greater than 80% repigmentation (Figure 2).

**Remarks on the lack of consensus on repigmentation scales**: Overall, the failure in terms of consensus (70% consensus is officially requested) of the e-delphi questionnaire on "scales to measure repigmentation", which was a success in terms of participation, highlights the limitations of this method compared to face-to-face meetings. Although the majority of participants (roughly 85%) agreed that there is a need for standardized/validated methods to evaluate vitiligo including disease severity and repigmentation, no consensus has been reached on a unified scale. Factors such as variation of expenses and concerns about the accuracy of the outcome measures may explain this lack of consensus. No consensus was also reached for the time at which the measurement of repigmentation should be performed. However, most of the responders agreed that a global scoring system such as the PASI for psoriasis is indeed needed in vitiligo. The discussion indicated that the e-delphi method has some flaws, especially: (i) the difficulty for opting out on the current e-delphi platform, for technical questions that are not related to the expertise of responders; (ii) the type of intervention may be considered more precisely in the questionnaire; (iii) expectations for treatments may differ greatly between patients and doctors in setting thresholds for outcome research; (iv) defining success on the basis of PASI 75/90 as for psoriasis could be dangerous and may discourage pharma-led projects and a more in-depth work on "success of intervention" is needed; (v) as stated in previous discussions, halting disease progression should be included in trials with unstable patients; (vi) the point of view of regulating authorities should be obtained on this matter (2 were present in the panel); (vii) a workshop evaluating patients should address the most important issues raised in the discussion.

**Recommendations/future directions**

Based on published data and discussions among VGICC panellists, some aspects of repigmentation in vitiligo need to be clarified before any standardization of outcome measures can be expected. The pattern and color match issues are tentatively solved in this position paper with the publication of an atlas. Concerning the techniques for measuring repigmentation, the current conclusion is that existing clinical instruments are overall lacking in accuracy and sensitivity to change. A practical, easy-to-administer instrument that is responsive to rapid and small improvements in repigmentation is needed. Future validation studies should be adequately powered and include patients with a range of Fitzpatrick skin phototypes and vitiligo severity. Instruments should ideally be validated against physician and patient assessments of repigmentation as well as against a digital image analysis tool for objective comparison.

The limitations of e-surveys have been shown when it comes to areas of clinical expertise, such as performing clinical measurements. As recommended by HOME (Harmonizing Outcomes Measures for Eczema) (Schmitt et al., 2015) and OMERACT (Boers et al., 2014), the consensus process should include, beyond the review of available instruments and e-delphi surveys, group discussion, plenary discussions, and confidential voting at face-to-face meetings. Therefore, the next envisaged step is to carefully prepare a workshop with patients, investigators and stakeholders, with the aim to answer a series of questions derived from the previous discussions. This workshop, the Vitiligo International Symposium, has been planned to take place in Rome, Italy in December 2016. The major questions to address are the following:

1. Comparing techniques for measuring extent (target lesion and BSA) with a reliable objective comparator, including inter-rater reliability and user-friendliness
2. Defining reliable techniques for assessment of light phototype patients
3. Consensus on minimal instrumental assessment: photographs and image analysis
4. Consensus on definition of objective global severity

**CONFLICT OF INTEREST**

There are no conflicts of interest to declare.

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## SUPPORTING INFORMATION

Appendix S1: Color Atlas: repigmentation patterns and color match

Appendix S2: List of e-delphi participants

## TABLES

Table 1 A summary of instruments used in measuring vitiligo repigmentation

| | Instrument | Description | Inter-rater reliability | Intra-rater reliability | Feasibility in trials | Feasibility in clinical practice | Reference |
|---|---|---|---|---|---|---|---|
| **A. Patient-reported outcomes** | | | | | | | |
| 1 | Vitiligo Life Quality Index (VLQI) | A series of 25 questions assessing various aspects of vitiligo's impact on a patient's life (skin types II to IV). | Not applicable | Test-retest scores were correlated (r=0.86, p<0.001). | Yes | Yes | Şenol et al., 2013 |
| 2 | Vitiligo Impact Scale-22 (VIS-22) | A series of 22 questions assessing the impact of vitiligo on a patient's life. | Not applicable | Test-retest scores were correlated (r=0.9053). | Yes | Yes | Gupta et al., 2014 |
| 3 | VitiQoL | A series of 16 questions assessing the impact of vitiligo on a patient's mental, emotional wellbeing and lifestyle practices in the last month. | Not applicable | Unknown | Yes | Yes | Lilly et al., 2013 |
| 4 | Vitiligo Noticeability Scale (VNS) | Patient rates the noticeability of vitiligo post-treatment compared with pre-treatment (score 1 to 5). | Not applicable | Unknown | Yes | Yes | Batchelor et al., 2016 |
| 5 | SAVASI (Self assessed Vitiligo Area Scoring Index) | Patient indicates the body parts affected by vitiligo, assesses the number of hand units affected per body part and extent of depigmentation within. | Not applicable | Test-retest scores had an intraclass correlation coefficient (ICC) 0.75 (95% CI 0.54-0.87). | Yes | Yes. 83% completed in less than 10 minutes. 8% assessed it to be hard. | Komen et al., 2015a |
| 6 | Vitiligo Impact Patient | A series of 35 questions in a specific vitiligo | Not applicable | Test-retest reliability was obtained | Yes | Yes | Salzes et al., 2016 |

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|---|---|---|---|---|---|---|---|
| | Scale (VIPs) | burden tool, customised according to skin phototype. | | in 2 groups – fair- and dark-skinned patients. ICC was >0.90 for each population and within each domain. | | | |
| 7 | Self-assessment Vitiligo Extent Score (SA-VES) | Patients assess the overall vitiligo involvement of the body (extent) by dividing the body into 12 separate areas. | Not applicable | ICC 0.948 (95% CI 0.911-0.970) | Yes | Yes | van Geel et al., in press |
| **B. Clinician-reported outcomes** | | | | | | | |
| 8 | Vitiligo Area Scoring Index (VASI) | Measures extent of depigmentation based on 5 separate and mutually exclusive body regions. | ICC 0.93, (95% CI 0.88 – 0.96) | ICC 0.93 (95% CI 0.86-0.97) | Yes | Yes | Hamzavi et al., 2004; Komen et al., 2015b |
| 9 | Vitiligo European Task Force Assessment (VETF) | Measures extent, stage and spreading of disease. | ICC 0.88 (95% CI 0.79-0.94) | ICC 0.97 (95% CI 0.94-0.99) | Yes | Yes | Taïeb et al., 2007; Komen et al., 2015b |
| 10 | Vitiligo Extent Score (VES) | Measures the overall vitiligo involvement of the body (extent) by dividing the body into 19 separate areas. | ICC 0.924 (95% CI 0.862-0.965) for live patients scoring. | ICC 0.943 (95% CI 0.897-0.974) for test-retest on pictures. | Yes | Yes | van Geel et al., 2016 |
| **C. Observer-reported outcomes** | | | | | | | |
| 11 | Digital Image Analysis System (DIAS) | Performs surface measurement of vitiligo lesions. | Coefficient of variation showed significant improvement of reproducibility for DIAS compared to visual estimation (p=0.01) | | Yes[1] | Yes[1] | van Geel et al., 2004 |
| 12 | Computerised digital imaging system (C-DIAS) | Technique based on principal component and independent component analyses to represent skin areas based on melanin and hemoglobin composition. | Unknown | Unknown | Yes[1] | Yes[1] | Shamsudin et al., 2015; Ahmad Fadzil et al., 2009; Nugroho et al., 2007 |
| 13 | Automated digital | A novel software program combining | No significan | Intra-rater variability | Yes[1] | Yes[1] | Sheth et al., 2015 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | image analysis system | standard image-processing techniques and image segmentation sensitive enough to detect differences in lesion area as low as 1%. | t difference between automated and manual methods. | was zero. | | | |
| 14 | 3D-imaging and analysis | Quantifies vitiligo affected body surface area by analyzing 3D whole-body images of vitiligo patients. | ICC 0.89 (95% CI 0.67-0.97) | ICC >0.95 for 3 raters. | Yes[2] | Yes[2] | Kohli et al., 2015 |

[1]Requires commercialization of end-user software and purchase of a good quality digital camera.
[2]Requires commercialization of end-user software and purchase of the high-resolution Canfield Vectra Whole Body 360 system (WB360).

**FIGURE LEGENDS AND FIGURES**

Figure 1

**Possible mechanisms occurring in repigmentation of vitiligo skin**

1. Migration of melanocytes from the borders of the non lesional skin
2. Differentiation and migration of melanoblasts from the hair follicle and sebaceous gland
3. Differentiation and migration of melanoblasts from the sweat glands
4. Differentiation and migration of melanoblasts from the dermis of glabrous skin

Under exposure to ultraviolet radiations, keratinocytes and to a lesser extent, fibroblasts produce differentiation, growth and migration factors that induce the differentiation of melanoblasts into melanocytes and stimulate their proliferation and migration from the different stem cell reservoirs of the skin.

Figure 2

**Definition of successful percentage of repigmentation.** The e-delphi panellists were asked to choose an image which defines successful percentage of pigmentation.

Results: Only 100%: 12/94 (13%); 90-100%: 30/94 (32%); 80-100%: 16/94 (17%); 75-100%: 20/94 (21%); 50-100%: 8/94 (8.5%); 25-100%: 1/94 (1%); Any repigmentation (i.e. 1-100%): 7/94 (7.5%)