

Recently, CD133 was detected in subsets of neoplastic cells in human primary cutaneous squamous cell carcinomas (SCCs) with TIC characteristics (Patel *et al.*, 2012), which raises two important questions regarding the significance of CD133 in non-melanoma skin cancer. First, do CD133⁺ SCC-initiating cells descend from transformed CD133⁺ keratinocyte hair follicle stem cells? Second, are there common regulatory mechanisms that underlie the regenerative and self-renewal capacities of normal and neoplastic CD133⁺ keratinocytes? Recent studies using genetic pulse-chase labeling approaches to genetically tag epidermal stem cells have helped to address the first question by demonstrating that bulge stem cells are susceptible to oncogenic Ras and serve as a cell of origin for SCCs, whereas transit cell populations are unable to initiate SCCs under the same conditions (reviewed in Thieu *et al.*, 2012). As for the latter question, the further characterization of the CD133⁺ bulge stem cell subset may be critical to our understanding of the cellular basis for SCC initiation and progression.

In summary, Charruyer and colleagues (2012) have presented significant advances to the field of cutaneous keratinocyte stem cells, including a pair of new selectable markers that represent a subset of $\alpha 6^{+}$ CD34⁺ label-retaining cells and a new *in vivo* limiting dilution assay for keratinocyte stem cells with long-term repopulating ability. This work has important implications for keratinocyte stem cell identification, culture, and assay, as well as for identifying the target cells in the pathogenesis of non-melanoma skin cancer.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Out of the Skin of Babies: Measuring the Full Impact of Atopic Dermatitis in Infants and Young Children

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Valid psychometric instruments should be culturally adapted and refined with use. Neri *et al.* present an excellent example of this process for the Childhood Atopic Dermatitis Impact Scale. The work emphasizes that psychometric measurement continues to develop and reminds us that optimal care of children with atopic dermatitis requires considering its multidimensional effects on both the children and their families.

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Atopic dermatitis (AD) manifests initially during the preschool years in ~90% of affected individuals and has been shown

to have a significant impact on the quality of life (QOL) of patients and their families (Chamlin and Chren, 2010).

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Clinical Implications

- To evaluate treatment strategies for Atopic dermatitis (AD) in children, researchers must measure validly AD's broad effects on patients and their families.
- Childhood Atopic Dermatitis Impact Scale (CADIS), the 45-item CADIS tool developed in the United States to measure the quality-of-life effects of atopic dermatitis on young children and their families has been adapted for Italian patients, and a shortened 33-item version has evidence of reliability and validity.
- Clinicians who care for young children with atopic dermatitis should consider children's symptoms and activity limitations, as well as parents' emotions, family and social function, and parents' sleep.

Pruritus in infants and young children has been associated with increased irritability, crying, clingy behavior, excessive dependency, and fearfulness. Young children with AD experience difficulty in falling asleep, restless sleep, and frequent night waking, which translate into daytime sleepiness, restlessness, and disruptive behavior that can be mistaken for learning disabilities and behavioral abnormalities. The physical, emotional, social, and financial impact of AD on the family of a young child is also significant. In 30% of families of young children with AD, the child's sleep disturbance is managed by co-sleeping (bed or room sharing with the parent) (Chamlin *et al.*, 2005b), which leads to parental sleep deprivation, often because the parents stroke the child's skin or hold the child's hands throughout the night to prevent them from scratching. The total hours of lost sleep for parents average upto 1–2 hours per night, in addition to the 2–3 hours spent daily in caring for their child (Su *et al.*, 1997). To help cope with the needs of the child, parents often make financially stressful changes in their lifestyle and home environment. Parents often experience sadness, worry, and self-blame (especially if they also have atopy) because of their child's AD. These emotions are exacerbated by the negative reactions and unsolicited advice from friends, relatives, and strangers. In their effort to avoid potential environmental triggers, minimize conflict, and care for their young children, AD parents of children often stay at home, which may increase their feelings of social isolation.

New interventions for treating AD and comparative effectiveness trials are desperately needed, including in affected young children. Assessment of the physical signs of AD is routine in these trials, using instruments such as SCORAD (Severity Scoring of Atopic Dermatitis) and EASI (Eczema Area and Severity Index). In the past decade, however, the impact of AD on QOL has been stressed, and instruments that measure QOL have increasingly been used (Rehal and Armstrong, 2011). The CDLQI (Children's Dermatology Life Quality Index) was developed and validated in 1995 as a variation of the DLQI to measure QOL in children aged 4 years and above, and it has been the most commonly used QOL scale for pediatric studies of skin disease. Its 10 questions address itching and sleep-loss issues, but also psychosocial effects on school performance, friendships, bullying, enjoyment of vacation, and participation in sports (Lewis-Jones and Finlay, 1995). For quantifying the effect of skin disorders on infants (0–4 years of age), the IDQOL (Infants' Dermatitis Quality of Life Index) was developed in 2001 (Lewis-Jones *et al.*, 2001). As in the CDLQI, the IDLQI includes 10 questions that probe issues related to itching, sleep, play and family activities, mealtimes, mood, bathing and dressing, and parental assessment of disease severity. Additional QOL instruments specifically examine the effect of AD on the family (dermatitis family impact (DFI); Parent's Index of Quality of Life in Atopic Dermatitis (PIQoL-AD)); and Parents of Children with Atopic Dermatitis (PQoL-

AD) (Rehal and Armstrong, 2011). None of these scales individually, however, measures the multidimensional effects of AD on QOL in both young children and their parents.

To address this gap, Chamlin and colleagues developed, tested, and refined the Childhood Atopic Dermatitis Impact Scale (CADIS) in American patients (Chamlin *et al.*, 2005a; Chamlin *et al.*, 2007). CADIS is a hypothesis-based QOL tool to measure the effects of AD on the lives of children younger than 6 years and their parents. The 45-item instrument was developed from an explicit conceptual framework based on substantial qualitative input from families and expert medical professionals; because of this input, CADIS focuses considerably on the emotional aspects of AD, in addition to its symptoms and functional and social effects.

The relative paucity of studies of interventions in infants and young children has limited experience in clinical trials with CADIS, and, to our knowledge, the instrument has not been previously translated and adapted for other cultures. In addition, because it has 45 items, CADIS is more cumbersome to use than the other pediatric QOL scales, most of which have 10 questions. Recently, Neri *et al.* (this issue, 2012) tested the validity of CADIS outside of the United States, and used psychometric criteria to develop a shortened version of the instrument, which they tested for evidence of validity.

The Italian version of the CADIS was translated using standard international guidelines, and the investigators used strict disease definitions and valid measures of disease severity. Scores with the Italian CADIS were compared with those from existing, widely accepted scales, using *a priori* hypotheses about the degree of expected correlation. In addition, the investigators developed what they learned from the psychometric tests. For example, they did not simply report the elimination of items that failed to correlate significantly or exclusively with 'factors' (i.e., hypothesized concepts) that explained variance in patients' responses. Instead, they used the results to infer clues about possible cultural differences in Italian children or

families compared with those from the United States.

Despite the many strengths of Neri *et al.*'s report, we might understand more about the experiences of Italian families with more open-ended items that inquired about the effects of AD. These responses would permit us to know about effects that were not addressed in the CADIS, which is important for content validity of the Italian version. We might also learn whether some aspects for which the items were not psychometrically robust (such as avoiding photos or effects of childhood AD on parents' work) are more typical of Americans than Italians. An intriguing example of an aspect about which we want more qualitative information is that over 40% of Italian parents categorized the economic costs of the condition as 'high' (Table 1, in the Neri *et al.* (2012) manuscript). We are not given information to understand more about this experience, nor how it compares with those of American respondents in the original development and validation work on CADIS (most of whom had private health insurance and reported family incomes of >\$75,000).

The study is a good example of a methodologically rigorous adaptation and testing of a patient-reported instrument for a different country from the one in which it was developed. However, as the authors note, the CADIS was designed using classical test theory rather than approaches that use item response theory (IRT) methods, such as Rasch modeling. Although classical test theory has been the conventional approach to the development and refinement of psychometric tools used in clinical medicine, IRT is a next-generation quantitative methodology that among other attributes considers the "difficulty" of each item and permits the use of computerized adaptive testing techniques with which the patient responds to a highly tailored set of questions based on his or her previous answers (McHorney, 1997). IRT methods typi-

cally result in instruments that are more generalizable, which is a strength when tools are used in patients from different cultures. However, IRT testing requires larger samples compared with those studied in this work. In addition, it requires measurement of concepts that are unidimensional (i.e., single psychological attributes affect patients' responses). As demonstrated by the CADIS, the effects of AD on small children and their families are multidimensional.

The growing list of instruments for evaluation of AD has prompted the establishment of the HOME initiative (Harmonizing Outcome Measures for Eczema), which uses Delphi exercises to develop consensus-based sets of core outcome domains for AD for use in clinical trials and visit documentation (Schmitt *et al.*, 2011). This panel has begun to assess physician-determined clinical signs, patient symptoms, and long-term control of flares as core outcome domains, and shortly it will evaluate QOL scales as well. Although several 10-question instruments have already been used in trials that separately address the impact on infants (Infant's Dermatitis Quality of Life Index), young children (CDLQI), and parents (Dermatitis Family Impact questionnaire), future intervention trials for infants and children under 6 years of age should consider the use of the CADIS instrument as an assessment tool that includes impact on both the child and parents, particularly if additional simplification of the instrument is undertaken.

In routine clinical practice, even 10-question scales are too onerous for most practitioners. Nevertheless, the five domains of the CADIS instrument (Child Symptoms; Child Activity Limitations; Parent Emotions; Family and Social Function; and Parent Sleep) must be broached in our discussions with families. Focus only on the visible features of AD, such as the erythema and lichenification, without incorporation into our encounter of the "vital signs" (Chren, 2005) of dermatologic evaluation—the physical, emotional, and

functional impact of skin disease—may lead to treatment decisions that do not adequately address familial needs, thus reducing compliance and worsening clinical outcome.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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