Beyond *JAAD* October 2019: Articles of interest to dermatologists from the nondermatologic literature

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COMPARISON OF THE ACCURACY OF HUMAN READERS VERSUS MACHINE-LEARNING ALGORITHMS FOR PIGMENTED SKIN LESION CLASSIFICATION: AN OPEN, WEB-BASED, INTERNATIONAL, DIAGNOSTIC STUDY

The authors conducted a web-based, international diagnostic study in which human readers were asked to diagnose dermatoscopic images selected randomly in 30-image batches from a test set of 1511 images. The diagnoses from the human readers were compared with diagnoses from a group of 139 algorithms. Included in the disease set were 7 predefined categories: intraepithelial carcinoma including actinic keratoses and Bowen disease; basal cell carcinomas; benign keratinocytic lesions including solar lentigo, seborrheic keratosis, and lichen planus-like keratosis; dermatofibroma; melanoma; melanocytic nevus; and vascular lesions. Overall, algorithms outperformed human readers. Human readers who were described as experts with more than 10 years of experience achieved a mean of 18.78 correct answers, compared with 25.43 correct answers for the top 3 machine algorithms. The authors stress that a "real-world" situation of a full cutaneous examination affords the human examiner the ability to recognize "ugly-duckling" lesions. They issue the disclaimer that "our study is a simulation and deviates from a real-life situation. In a real-life setting, evaluation of skin lesions in not limited to a timeframe of 20 [seconds], and human readers might make different decisions when faced with a patient in person."

Tschandl P, Codella N, Akay B, et al. Comparison of the accuracy of human readers versus machine-learning algorithms for pigmented skin lesion classification: an open, web-based, international, diagnostic study. *Lancet.* 2019:20(7):938-947.

MORPHOLOGIC AND IMMUNOPHENOTYPICAL FEATURES DISTINGUISHING MERKEL CELL POLYOMAVIRUS-POSITIVE AND NEGATIVE MERKEL CELL CARCINOMA

Previous studies have identified Merkel cell polyomavirus integration as the primary oncogenic event in approximately 80% of Merkel cell carcinomas, with the remaining Merkel cell carcinomas likely caused by ultraviolet radiation. Virus-negative, ultraviolet radiation–induced Merkel cell carcinomas are characterized by worse outcomes than their virus-positive counterparts. The authors of this study compared the morphologic and immunohistochemical features of virus-positive versus virus-negative Merkel cell carcinoma cases. They found that virus-positive and virus-negative Merkel cell carcinomas are characterized by distinct morphologic and immunohistochemical features, implying a difference in tumor biology and behavior. Virus-negative cases were found to have more frequent positivity of TTF-1 and cytokeratin 7 and abnormal p53 expression. Virus-positive cases were found to be strongly associated with a CD99 dot-like pattern. The authors offer this last association as a surrogate for polyomavirus positivity or negativity and suggest the potential value of routine determination of virus status through testing for CD99 expression, given the increased aggressiveness and worse outcome of virus-negative cases.

Kervarrec T, Tallet A, Miquelestorena-Standley E, et al. Morphologic and immunophenotypical features distinguishing Merkel cell polyomavirus-positive and negative Merkel cell carcinoma. *Mod Pathol.* 2019. https://doi.org/10.1038/s41379-019-0288-7.

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PRAME EXPRESSION IN MELANOCYTIC TUMORS

Preferentially expressed antigen in melanoma (PRAME) is an antigen found in the testis that has a strong preferential expression in melanomas and is used in some assays to help diagnose melanoma. These authors looked at the immunohistochemical expression of PRAME in 155 primary melanomas and 100 metastatic melanomas and compared it with nevi of all types. Intense and diffuse staining (called 4+ by the authors) was found in more than 80% of all melanomas, except for the desmoplastic type. Nevi showed either no expression at all or less intense staining. The antigen also could be used for the delineation of margins and could help distinguish residual in situ disease from activated or photoactivated melanocytes. This marker could be a useful tool in the diagnosis and therapy of melanocytic tumors.

Lezcano C, Jungbluth AA, Nehal KS, et al. PRAME expression in melanocytic tumors. *Am J Surg Pathol.* 2018;42(11):1456-1465.

A PROSPECTIVE STUDY OF TOENAIL TRACE ELEMENT LEVELS AND RISK OF SKIN CANCER

Toenail levels of mercury, selenium, chromium, iron, and zinc were measured from 6708 women in the Nurses' Health Study (1984-2012) and 3370 men in the Health Professionals Follow-up Study (1986-2012). Participants were free of skin cancer at the time of toenail collection and were subsequently followed for incident basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma. During the 26-28 years of follow-up, 2,433 BCC, 334 SCC, and 130 melanoma cases were identified. The authors found a positive association between toenail mercury levels and risk of BCC for both women and men. They also found direct associations for SCC and melanoma but with limited statistical power. Of interest is the fact that fish intake is the major source of mercury exposure in the United States and that fish intake was similarly positively associated with BCC risk. The authors suggest that exposure to mercury may increase skin cancer risk, and they call for further studies and for further investigation of relevant biological mechanisms.

Matthews N, Koh M, Wen-Qing L, et al. A prospective study of toenail trace element levels and risk of skin cancer. *Cancer Epidemiol Biomarkers Prev.* June 19, 2019. https://doi.org/10.1158/1055-9965.EPI-19-0214

EFFECT OF SUNSCREEN APPLICATION UNDER MAXIMAL USE CONDITIONS ON PLASMA CONCENTRATION OF SUNSCREEN ACTIVE INGREDIENTS—A RANDOMIZED CLINICAL TRIAL

The US Food and Drug Administration, in its monograph "Guidance for Industry: Nonprescription Sunscreen Drug Products Safety and Effectiveness Data," suggests that nonclinical toxicology studies (eg, systemic carcinogenicity and additional developmental and reproductive studies) may be waived if the results of an adequately conducted human pharmokinetic maximal use trial show a steady-state blood level of less than 0.5 ng/mL and if an adequately conducted toxicology assessment does not show any potential safety concerns. The authors studied this question by dividing 24 study participants into 4 groups and applying 1 of 4 sunscreens to the members of each group. The sunscreens were applied to 75% of the body surface, 4 times daily for 7 days. Ingredients of the 4 sunscreens included avobenzone, oxybenzone, octocrylene, and ecamsule. Plasma concentrations of each of those ingredients exceeded the US Food and Drug Administration's threshold in all 4 groups. Limitations of the study included the small sample size and the facts that application took place indoors and that the study participants were not exposed to heat, sunlight, or humidity, which in a real-life situation might alter or modify sunscreen ingredient absorption. The authors suggest that further studies be done to determine the clinical significance of their findings, and they stress that "these results do not indicate that individuals should refrain from the use of sunscreen."

Matta M, Zusterzeel R, Nageswara R, et al. Effect of sunscreen application under maximal use conditions on plasma concentration of sunscreen active ingredients—a randomized clinical trial. *JAMA.* 2019;321(21):2082-2091.

RELATIONSHIP BETWEEN SUN SAFETY BEHAVIORS AND MODIFIABLE LIFESTYLE CANCER RISK FACTORS AND VITAMIN D LEVELS

The authors examined the relationship between sun protection behaviors and modifiable lifestyle risk factors for other cancers. Using data from 2 large Canadian health surveys, they found that unhealthy lifestyle risk factors such as cigarette consumption, secondhand smoke exposure, higher alcohol consumption, use of street drugs, not having a regular doctor, and low levels of fruit and vegetable consumption were associated with sunburns and risky sun safety behavior. The authors also found that 39.2% of individuals studied had lower-than-normal vitamin D levels despite significant sun exposure. They point out that because sun exposure does cause skin cancer and that they had previously reported that adequate vitamin D levels are not feasibly produced with sun exposure during the fall and winter months in Canada, a safe vitamin D strategy would involve vitamin D–rich foods and supplements as a reliable source and without adverse

skin cancer effects. In closing, the authors suggest that when designing skin cancer prevention campaigns, communicators take note of the high correlation of modifiable risk factors for other cancers and consider the fact that campaigns taking a more generalized cancer preventative approach may be more cost effective.

Kalia S, Kwong Y. Relationship between sun safety behaviours and modifiable lifestyle cancer risk factors and vitamin D levels. *Photodermatol Photoimmunol Photomed,* in press. https://doi.org/10.1111/phpp.12494.

ASSOCIATION OF INDOOR TANNING EXPOSURE WITH AGE AT MELANOMA DIAGNOSIS AND *BRAF* V600E MUTATIONS

The authors investigated indoor tanning use in patients with melanomas in sun-exposed skin and studied the clinicopathologic and molecular characteristics of the melanomas in relation to indoor tanning exposure history. Patients from a clinic for cutaneous cancers completed standardized questionnaires on risk factors for melanoma as part of their medical history at intake. The 114 patients who reported indoor tanning exposure were younger at diagnosis than the 222 patients who reported no indoor tanning (51.5 vs 64.0 years). *BRAF* 600E genotype was more prevalent in ever users than in nonusers (42.9% vs 28.3%) and was higher in ever users who initiated indoor tanning before age 25 years compared with age 25 years or older (62.2% vs 31.1%). There were also more melanomas in intermittently sun-exposed skin in ever users than in nonusers (65.7% vs 51.9%). Finding that indoor tanning exposure is associated with melanomas in intermittently sun-exposed skin, younger age at diagnosis, and *BRAF* V600E mutations, the authors state that their data suggest that indoor tanning may promote melanomas that arise in skin with low chronic-sun–induced damage through *BRAF* V600E–mediated melanogenesis.

Burgidge TE, Bastian BC, Guo D, et al. Association of indoor tanning exposure with age at melanoma diagnosis and *BRAF* V600E mutations. *J Natl Cancer Inst.* 2019;111(11):djz048.

RISK FACTORS AND OUTCOMES IN NONMELANOMA SKIN CANCER IN CHILDREN AND YOUNG ADULTS

Nonmelanoma skin cancer (NMSC) is uncommon in children absent known risk factors. Investigators from 11 academic centers sought to identify associated risk factors and survival in this retrospective case-control study. A total of 124 patients younger than 20 years of age were identified with NMSC (40 with basal cell carcinoma, 90 with squamous cell carcinoma, 4 with both), and 70% had at least 1 identifiable risk factor. Risk factors included genetic conditions such as basal cell nevus syndrome and xeroderma pigmentosa, predisposing skin lesions such as chronic ulcers and nevus sebaceous, and iatrogenic exposures such as chemotherapy or voriconazole. Nearly half (48%) of NMSCs had been present for longer than 1 year before initial diagnosis, and 5% of the patients died, although only 1 died of skin cancer or associated therapy. Overall, 44% of patients had never seen a dermatologist at the time of initial diagnosis. The authors advocate for identification of high-risk patients and appropriate early counseling and management.

Huang JT, Coughlin C, Hawryluk E, et al. Risk factors and outcomes in nonmelanoma skin cancer in children and young adults. *J Pediatr.* 2019;211:152-158.

THE EXPOSOME IN ATOPIC DERMATITIS

In the journal *Cancer Epidemiology and Biomarkers* in 2005, cancer epidemiologist Christopher Paul Wild suggested that "there is a need for an 'exposome' to match the 'genome.'" "At its most complete," he wrote, "the exposome encompasses life-course environmental exposures (including lifestyle factors), from the prenatal period onwards." Wild compared the current reliance on genotyping in our understanding of disease to the anatomy of the fiddler crab, with one claw (genotyping) hypertrophied and the other claw (the study of the external environment) atrophied. The authors of this review undertakes to build up the other claw of our understanding of atopic dermatitis, which has been traditionally understood as a genetic predisposition, but is, on further examination, a product of many nongenetic influences and determinants. The authors examines the skin-gut connection, dietary influences, the cutaneous microbiome, the role of allergens and allergic sensitization, water hardness or softness, environmental pollution, ultraviolet radiation, temperature and humidity, and psychological stress during not just postnatal but prenatal life in their respective roles in the phenomenon of atopic dermatitis. They stress the importance of monitoring all of these factors over time and call for "novel approaches and study methodology, such as longitudinal monitoring of individuals to capture specific exposures together and the use of artificial intelligence," suggesting wearable sensors to record an individual's specific exposures. They propose that "by studying the pathways downstream of various doses of exposures at various times both pre and post-natally an optimum set of exposures may emerge, enabling a

degree of definitive prevention or symptom amelioration in [atopic dermatitis]."

Stefanovic N, Flohr C, Irvine, A. The exposome in atopic dermatitis. *Allergy*. 2019. https://doi.org/10.1111/all.13946.

ASSOCIATION OF ATOPIC DERMATITIS WITH SLEEP QUALITY IN CHILDREN

Sleep disturbance is a common challenge for children with atopic dermatitis (AD). Ramirez and colleagues used a longitudinal cohort of 13 988 children followed for a mean duration of 11 years to quantify the impact of AD on sleep duration and quality. Although no statistical difference was found in sleep duration, children with AD had markedly more disrupted sleep, including nighttime and early awakening, difficulty falling asleep, and nightmares. Children with severe AD and those with comorbid asthma experienced even greater effects on sleep (adjusted odds ratio of sleep disruption, 1.79; 95% confidence interval, 1.54-2.09). Nighttime scratching accounted for only 15% of arousals and awakenings, consonant with the belief that sleep fragmentation is multifactorial. Heightened sensitivity to cutaneous stimuli likely contributes to the problem. Because poor sleep has been linked to negative developmental and psychosocial outcomes, pediatricians and dermatologists who care for children with AD should screen for sleep disturbance.

Ramirez FD, Chen S, Langan SM, et al. Association of atopic dermatitis with sleep quality in children. *JAMA Pediatr*. 2019;173(5):e190025.

CORTICOSTEROID PHOBIA (CORTICOPHOBIA) IN PARENTS OF YOUNG CHILDREN WITH ATOPIC DERMATITIS AND THEIR HEALTH CARE PROVIDERS

Corticosteroid phobia is a well-documented barrier to treatment compliance in caregivers of young children with atopic dermatitis. Bos et al investigated the prevalence of corticosteroid phobia among health care professionals in The Netherlands to better understand the depth of the problem. A validated instrument to quantify corticosteroid phobia, Topicop, was used to evaluate parents of children with atopic dermatitis aged 0 through 5 years at a single center. Health care providers, including public health nurses, general practitioners, and general pediatricians, were also studied. Public health nurses and parents had identical levels of corticosteroid phobia (44%), and the lowest level of phobia was seen in pediatricians (31%). These data remind us that if dermatologists want to successfully address corticosteroid phobia, education must apply to all groups involved in patient care.

Bos B, Antonescu I, Osinga H, et al. Corticosteroid phobia (corticophobia) in parents of young children with atopic dermatitis and their health care providers. *Pediatr Dermatol*. 2019;36:100-104.

THE NONLESIONAL SKIN SURFACE DISTINGUISHES ATOPIC DERMATITIS WITH FOOD ALLERGY AS A UNIQUE ENDOTYPE

Atopic dermatitis (AD) is a heterogeneous disease. However, clinically, investigators have been unable to identify a reliable biomarker that correlates with the diverse phenotypes. Leung and colleagues used a skin tape-stripping method to compare lipid, protein, and transcriptome profiles in 3 separate groups: children with AD and food allergies (ADFA+); children with AD but no food allergies (ADFA-); and healthy control individuals. Nonlesional skin in the ADFA+ cohort was found to have increased transepidermal water loss, fewer filaggrin breakdown products, and decreased lipid content such as ceramide when compared with ADFA- and control patients. Additionally, nonlesional ADFA+ skin was found to have increased *Staphylococcus aureus* colonization compared with normal-appearing control skin. These findings identify children with AD and food allergies as a potentially unique endotype. The fact that the abnormalities were identified in nonlesional skin suggests that such patients are at risk for cutaneous sensitization over the entire skin surface.

Leung DYM, Calatroni A, Zaramela L, et al. The nonlesional skin surface distinguishes atopic dermatitis with food allergy as a unique endotype. *Sci Transl Med*. 2019;11(480):eaav2685.