dermatologic use and among specific dermatologist subgroups. Use trends of nonbiologic immunosuppressants were also characterized.

From 2013 to 2017, total annual claims for biologics by dermatologists increased at a mean annual rate of 11.0% compared with 4.8% for traditional immunosuppressants. Adalimumab was the most frequently used biologic, with apremilast demonstrating the highest growth rate (Table I). Greater annual increases in biologic claims occurred among younger dermatologists, those in the Northeast, and those in counties with a greater population density and median income (Table II).

These findings support that growth in biologic use has outpaced that of traditional therapies across many subsets of dermatologists, although conventional therapies still play an important dermatologic role. As a class, biologic agents are well tolerated, are generally more efficacious than conventional treatments,[2] and improve patient satisfaction,[3] all of which may promote their use. Off-label trials may also be driving prescriptions for several agents, especially tumor necrosis factor α inhibitors, for difficult-to-treat skin conditions.[1]

Claims for etanercept diminished during the study period, which could be due to the increasing use of agents with comparably greater efficacy (eg, secukinumab, ustekinumab) or a more convenient administration route (eg, apremilast).[2] Dupilumab was modestly used in 2017 after its approval, but may play a more substantial role in coming years amid increasing supportive evidence.[1]

Greater biologic use among older dermatologists in small private practices could be driven by the high number of dermatologists and established patients in these settings. However, biologic adoption rates were greater among academic and younger dermatologists. The lower growth of biologic therapies in rural regions is concerning alongside prior evidence that demonstrated fewer biologic prescribers in these areas,[4] and may suggest a widening geographic access gap. Slower adoption of biologics in counties with dermatologist shortages and lower incomes may compound access limitations that already exist among underinsured and minority patients in these settings.

Because the study assessed Medicare data, it may not reflect claims to commercial payers. These data cannot be directly correlated to clinical outcomes. Despite limitations, these findings affirm widespread but nonuniform growth of biologic agents among dermatologists. Although this study did not specifically assess payments, the findings should be interpreted in the context of high costs and persistent price increases for biologics.[5] As the clinical value of biologics continues to expand, efforts to further characterize and ensure appropriate access to these novel therapies are warranted.

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Impact of ethnicity on the diagnosis and management of cutaneous toxicities from immune checkpoint inhibitors

To the Editor: Immune checkpoint inhibitors (ICIs) have improved outcomes for numerous malignancies,

Table I. Features of patients receiving ICIs (N = 2447) and associated cirAEs (n = 358)

Characteristics of patients receiving ICIs	Overall (N = 2447)	White (n = 2189)	Nonwhite (n = 181)	*P* value*
Age, y, median (IQR)	65 (57-73)	66 (58-74)	59 (50-69)	<.001
Female sex, n (%)	1064 (43.5)	949 (43.4)	72 (39.8)	.390
Self-reported race, n (%)				
White	2189 (89.5)	2189 (100.0)	—	
Asian	93 (3.8)	—	93 (51.4)	
Black or African American	55 (2.2)	—	55 (30.4)	
Other†	33 (1.3)	—	33 (18.2)	
Unknown	77 (3.1)	—	—	
Cancer type, n (%)				.002‡
Melanoma	513 (21.0)	493 (22.5)	6 (3.3)	
Thoracic	817 (33.4)	727 (33.2)	64 (35.4)	
GI	288 (11.8)	239 (10.9)	38 (21.0)	
Head or neck	236 (9.6)	198 (9.0)	31 (17.1)	
Other§	593 (24.2)	532 (24.3)	42 (23.2)	
ICI regimen				
PD-1/PD-L1	2170 (88.7)	1934 (88.4)	169 (93.4)	.056
CTLA-4	42 (1.7)	39 (1.8)	0 (0.0)	
PD-1/PD-L1 + CTLA-4	235 (9.6)	216 (9.9)	12 (6.6)	
Diagnosed cirAE, n (%)‖	358 (14.6)	335 (15.3)	13 (7.2)	.002

Characteristic of first diagnosed cirAE episode	Overall (N = 358)	White (n = 336)	Nonwhite (n = 13)	*P* value*
Time to cirAE, days, median (IQR)	51 (19-141)	49 (19-139)	105 (24-220)	.145
cirAE categorization				
Clinicopathologically precise, n (%)	154 (43.0)	142 (42.3)	9 (69.2)	.088
Isolated pruritus	68 (19.0)	65 (19.3)	2 (15.4)	
Eczematous	23 (6.4)	21 (6.3)	1 (7.7)	
Lichenoid	14 (3.9)	13 (3.9)	0 (0.0)	
Psoriasiform	12 (3.4)	10 (3.0)	2 (15.4)	
Other¶	37 (10.3)	33 (9.8)	4 (30.8)	
Clinicopathologically imprecise, n (%)#	204 (57.0)	194 (57.7)	4 (30.8)	—
Peak cirAE CTCAE (version 5.0) grade, median (IQR)**	1 (1-2)	1 (1-2)	1 (1-1)	.063
Referral to dermatology specialist for cirAE, n (%)	111 (31.0)	101 (30.1)	8 (61.5)	.028
Most potent cirAE treatment, n (%)				.248
None or supportive care only	97 (27.1)	92 (27.4)	2 (15.4)	
Nonsteroid topical therapy	4 (1.1)	4 (1.2)	0 (0.0)	
Oral antihistamine	65 (18.2)	60 (17.9)	3 (23.1)	
Topical corticosteroids	142 (39.7)	130 (38.7)	8 (61.5)	
Systemic corticosteroids	50 (14.0)	50 (14.9)	0 (0.0)	

cirAE, Cutaneous immune-related adverse event; *CTCAE*, Common Terminology Criteria for Adverse Events; *CTLA-4*, cytotoxic T-lymphocyte antigen 4; *GI*, gastrointestinal: *ICI*, immune checkpoint inhibitor; *IQR*, interquartile range; *PD-1*, programmed death 1; *PD-L1*, programmed death ligand 1.

**P* values provided reflect the univariate outputs of Fisher's exact tests for categorical variables and Wilcoxon's rank sum tests for continuous variables. The 77 patients for whom race was unknown, including 9 who developed a cirAE, were excluded from analyses comparing groups by patient-reported race.

†Included 1 patient identifying as Hawaiian or other Pacific Islander; the remainder of the patients in the *other* category self-reported other race without further available detail.

‡Because of the limited sample size of patients with some cancer types, the reported *P* value is associated with the statistical comparison of patients with cancers associated with a high baseline cirAE incidence of greater than 30% (namely, patients with melanoma and head and neck cancers) compared to those with other cancer types.[3]

§Includes the following malignancies (overall n [%], white n [%], nonwhite n [%]): genitourinary (n = 183 [7.5], n = 170 [7.7], n = 11 [6.1]), gynecologic (n = 131 [5.4], n = 117 [5.3], n = 11 [6.1]), hematologic (n = 112 [4.6], n = 101 [4.6], n = 6 [3.3]), neurologic (n = 92 [3.8], n = 80 [3.7], n = 6 [3.3]), breast (n = 57 [2.3], n = 49 [2.2], n = 7 [3.9]), and sarcoma (n = 18 [0.7], n = 15 [0.7], n = 3 [0.6]).

‖Provided information delineates features of patients' first diagnosed cirAE episode. cirAEs were defined as cases of isolated pruritus or cutaneous eruption emerging after ICI initiation, consistent with established morphologic categories, lasting longer than 1 day, affecting more than 1% body surface area, and attributed to ICI by the evaluating clinician.[5]

¶Includes the following cirAE categorizations (overall n [%], white n [%], nonwhite n [%]): vitiligo (n = 9 [2.5], n = 7 [2.1], n = 2 [15.4]), mucositis (n = 9 [2.5], n = 9 [2.7], n = 0 [0.0]), bullous (n = 7 [2.0], n = 7 [2.1], n = 0 [0.0]), erythema multiforme (n = 4 [1.1], n = 3 [0.9], n = 1 [7.7]), urticarial (n = 4 [1.1], n = 4 [1.2], n = 0 [0.0]), panniculitis (n = 2 [0.56], n = 1 [0.3], n = 1 [7.7]), Stevens-Johnson syndrome/toxic epidermal necrolysis (n = 1 [0.28], n = 1 [0.3], n = 0 [0.0]), and Sweet syndrome (n = 1 [0.28], n = 1 [0.3], n = 0 [0.0]).

#Includes the following cirAE categorizations (overall n [%], white n [%], nonwhite n [%]): maculopapular (n = 179 [50.0], n = 170 [50.6], n = 3 [23.1]), hypersensitivity reaction not elsewhere classified (n = 17 [4.8], n = 17 [5.1], n = 0 [0.0]), and acneiform/follicular (n = 8 [2.2], n = 7 [2.1], n = 1 [7.7]).

**The peak severity of CTCAE represents the highest grade reported by any evaluating physician. Minimum and maximum severity grades (minimum, maximum) for each category are as follows: overall (1, 4), white (1, 4), and nonwhite (1, 3).

Table II. Differences in cirAE diagnosis, referral, and treatment patterns by patient-reported race

Outcome*	OR†	SE	95% CI	*P* value
Rate of cirAE diagnosis	0.502	0.151	0.278-0.905	.022§
Precision of cirAE diagnosis	2.360	0.271	0.671-8.305	.115
Severity of diagnosed cirAE‡	2.749	2.187	0.578-13.074	.204
Referral for cirAE	5.537	3.461	1.627-18.850	.006§
Any treatment of cirAE	2.749	2.187	0.578-13.074	.204
Potency of cirAE treatment	1.333	0.680	0.490-3.622	.574

CI, Confidence interval; *cirAE*, cutaneous immune-related adverse event; *OR*, odds ratio; *SE*, standard error.

*For all models other than potency of cirAE treatment, binary logistic regression was used. For potency of cirAE treatment, ordered logistic regression was used.

†Reference category for all models is patient-reported race category of "white." The 77 patients for whom race was unknown, including 9 who developed a cirAE, were excluded from analyses.

‡For nonwhite patients referred to a dermatology specialist, the median grade for cirAE severity as 1 (interquartile range, 1-1) with psoriasiform and vitiliginous being the most common morphologies. For referred white patients, the median grade for cirAE severity was 2 (interquartile range, 1-3), with eczematous, hypersensitivity, maculopapular rash, and lichenoid being the most common morphologies.

§All models included patient-reported race, age, sex, and additional clinical features significant to $P < .10$ as covariates, with details as follows for each model. Rate of cirAE diagnosis: age, sex, cancer type, and immune checkpoint inhibitor type. Time to cirAE diagnosis: age and sex. Precision of cirAE diagnosis: age, sex, and referral to a dermatology specialist. Severity of diagnosed cirAE: age and sex. Referral for cirAE: age, sex, cancer type and cirAE severity. Any treatment for cirAE and potency of cirAE treatment: age, sex and cirAE severity.

but their benefits remain unevenly distributed across patient populations.[1-3] Among patients with cancer, racial disparities have been documented for an array of clinical outcomes, including time to diagnosis and rate of ICI delivery.[1,2] However, whether similar differences exist with regard to the diagnosis and treatment of immune-related adverse events (irAE) remains underexplored.[4] Differences may be particularly significant for skin toxicities because cutaneous immune-related adverse events (cirAEs) are heterogeneous and require diagnostic expertise to identify.[5] Although it is established that cirAEs are underdiagnosed and resources for different skin phototypes are underdeveloped, little is known regarding the interplay between these factors.[5] We sought to address this gap by examining whether patterns of cirAE diagnosis, referral, and treatment differed by patient-reported race.

We used the Research Patient Data Registry and billing data to obtain demographics (including patient-reported census race category), oncologic history, and plausible cirAE status for all patients who received ICIs at Massachusetts General Hospital between January 1, 2016, and March 8, 2019. cirAE status, morphology, and severity were subsequently confirmed by chart review using established criteria (Supplemental Materials; available via Mendeley at https://doi.org/10.17632/m689r3v4r3.1).[5] We then used logistic regression to assess differences in cirAE diagnosis, referral, and treatment patterns by patient-reported race. All multivariate models included age, sex, and covariates significant to $P < .10$.

Between 2016 and 2019, 2447 patients (median age, 65 years; 43.5% female) received ICIs (n = 2170; 88.7% PD-1/PD-L1) (Table I). Patient-reported race categories included white (n = 2189; 89.5%), Asian (n = 93; 3.8%), black or African American (n = 55; 2.3%), other (n = 32; 1.3%), and unknown (n = 77; 3.1%). In multivariate models adjusted for age, sex, ICI regimen, and cancer type, nonwhite patients were half as likely to be diagnosed with a cirAE compared to white patients (odds ratio = 0.501; $P = .022$; 95% confidence interval, 0.278-0.905) (Table II). The severity and precision of cirAE categorization did not differ significantly among groups. Regarding cirAE management, nonwhite individuals were also nearly 6 times more likely to be referred to a dermatology specialist (OR = 5.537; $P = .006$; 95% confidence interval, 1.627-18.850) than white individuals (Table II). The rates and potencies of treatment across groups were similar.

This study provides a novel characterization, to our knowledge, of cirAE diagnosis, referral, and treatment patterns across patient-reported race categories. In alignment with prior work showing similar irAE incidence by race, we observed similar cirAE morphologies and severities among white and nonwhite patients.[4] However, we also found that nonwhite patients were half as likely to be diagnosed with a cirAE and nearly 6 times more likely to be referred to a dermatology specialist for cirAE management than white patients.[1,2] Collectively, these findings underscore differences in the processes of cirAE care delivery by race that cannot be adequately accounted for by intrinsic cirAE features. Comprehensive point-of-care resources supporting cirAE management across phototypes merits further development. Limitations of this study include its retrospective design and the small number of nonwhite patients, which may have influenced our ability to measure and account for all possible confounding factors. Despite these limitations, our work illuminates important differences in cirAE parameters by patient-reported race, highlighting opportunities for resource diversification and further optimization of oncologic care.

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Translational research on the role of formula stability in Hetter's phenol–croton oil peels: Analysis of chemical studies and clinical outcomes from a randomized, double-blinded, split-face controlled trial

To the Editor: Phenol–croton oil formulas contained Septisol (SEP) (Steris, Mentor, OH), a discontinued antiseptic handwash that contained sodium C14-16 olefin sulfonate as the surfactant.[1] Currently, PEG-80 sorbitan laurate, Novisol, (NOV) (Young Pharmaceuticals, Wethersfield, CT) has been adopted by some specialists because of improved chemical stablility.[2-4] Before NOV, we explored the use of Johnson's baby shampoo (JBS) (Johnson & Johnson do Brasil, São Paulo, Brazil), which contains a long list of surfactants. We aimed to characterize the role of formula stability in 1.2% croton oil in 35% phenol peels[5] mixed with SEP or JBS.

Chemical studies were performed by macroscopy, microscopy, and zeta potentials analysis (see Supplement 1, available via Mendeley at https://doi.org/10.17632/n5n5mfkkhb.1). A clinical study was performed by a split-face, double-blind, randomized trial that enrolled 12 women (skin types I-III) for the treatment of photoaging (Glogau types III-IV) (see Supplement 2 available via Mendeley at https://doi.org/10.17632/kbhjfzsgk2.1). Three blinded graders scored baseline and 6-month postprocedure photographs. Efficacy was evaluated by using a validated photonumeric scale, and safety was evaluated by irregularity of results, defined as 1 side showing increased contrast between areas of persistent photoaging and areas of smooth texture (see Supplement 3 available via Mendeley at https://doi.org/10.17632/2fj4y7gpv9.1).

Both the SEP and JBS formulas were unstable biphasic dispersions. Charge distribution was not maintained during the first minute after homogenization, indicating high droplet movement and coalescence. Dispersion instability was observed macroscopically and microscopically with almost immediate phase separation. Unstable dispersions exhibited rapid coalescence of active droplets (phenolic phase) (Supplemental Video 1 available on jaad.org). This accelerated coalescence results in a concentrated lower layer within the first minute (Fig 1). Clinically, although similar improvement was observed ($P < .000001$) for both SEP and JBS, JBS presented the most irregular results, in 68% of the blinded evaluations versus 32% for SEP ($P = .050$). One patient developed bilateral leucodermic superficial scars.

Lack of stability produces a higher-than-intended concentration of active ingredients in the lower part of the cotton-tipped applicator within seconds (JBS > SEP), which translates into increased action in some areas throughout the procedure and irregular results (making JBS less safe than SEP) (Fig 2). Emulsion stability improved the efficacy and safety of phenol–croton oil formulas in vivo.[1] One example was presented in a recent illustrative case that showed irregular distribution of prolonged healing zones with SEP, whereas with NOV, the healing was uniform.[4] In spite of areas of prolonged healing, possibly due to the increased depth with SEP,[4] the final results with the more stable NOV