Table I. Risk of diabetes in Darier disease*

		Diabetes type 1			Diabetes type 2		
Variable	No.	No. (%)	Male/female ratio	RR (95% CI)	No. (%)	Male/female ratio	RR (95% CI)
Darier disease	770	22 (2.86)	8/14	1.74 (1.13-2.69)	22 (2.86)	8/14	0.88 (0.57-1.36)
Without Darier disease	76,987	1,288 (1.67)	643/645		2,471 (3.21)	1,228/1,247	

CI, Confidence interval; *RR*, risk ratio.
*RRs and corresponding 95% CIs expressing associations between type 1 and type 2 diabetes in individuals with Darier disease compared with matched comparison individuals without Darier disease.

peak incidence for T1D is age 5 to 9 years,[3] thus preceding DD.

Several causes of T1D, including autoimmune inflammation, have been identified, and most of these are associated with ER stress.[4] ER stress and Ca^{2+} dysregulation may lead to altered posttranslational modifications of endogenous protein or to misfolded proteins and thus generate neoautoantigens, which could stimulate an autoimmune β-cell attack.[5] This study identifies a potential novel nonimmunity-related T1D risk factor and contributes to the appreciation of DD as a syndrome affecting organs other than the skin.

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A cross-sectional survey of knowledge, attitudes, and practice in the prescription of isotretinoin for transgender patients among academic dermatologists

To the Editor: Multiple reports have called attention to the complexity of assigning transgender patients to a category within the iPLEDGE system,[1-3] especially transgender men (female to male) receiving testosterone therapy who retain their reproductive organs and have the potential to become pregnant.[4] Prescribers must choose between enrolling transgender patients under the sex assigned at birth (which is discordant with the gender identity) or the gender they align with (which is noncompliant with iPLEDGE). Additionally, to accurately determine reproductive potential in transgender patients, dermatologists must be knowledgeable regarding the effects of hormonal treatments on fertility. This cross-sectional study was conducted to assess the knowledge, attitudes, and practice of academic dermatologists toward the prescription of isotretinoin for transgender patients.

After institutional review board approval (Johns Hopkins School of Medicine, approval no. 00145210), an anonymous 18-item survey was e-mailed to the 385 members of the Association of Professors of Dermatology, who were encouraged to distribute it to faculty and resident physicians. Respondents answered questions regarding

Table I. Responses to case-based scenarios

Case-based scenarios	Answer, %*
Case 1: You determine that a 24-year-old transgender man with acne would benefit from treatment with isotretinoin. At birth he was classified as female.	
He identifies as a heterosexual male and is in a monogamous relationship with a female. He denies current sexual intercourse with men. For gender dysphoria, he receives weekly intramuscular testosterone injections. He has been amenorrhoeic since he started these injections one year ago. He has not had any surgical interventions for his gender transition. He has legally changed his gender to male on his driver's license and in his medical record. How would you treat this patient?	
Treat with isotretinoin and register as male	11.2
Treat with isotretinoin and register as female of nonchildbearing potential	29
Treat with isotretinoin and register as female of childbearing potential	59.8
Do not offer treatment with isotretinoin	0
Case 2: You determine that a 24-year-old transgender man with acne would benefit from treatment with isotretinoin. At birth he was classified as female.	
He identifies as a gay male and is in a monogamous relationship with a male. For gender dysphoria, he receives weekly intramuscular testosterone injections and is amenorrhoeic but has no plans for surgical procedures. He has legally changed his gender to male on his driver's license and in his medical record. How would you treat this patient?	
Treat with isotretinoin and register as male	10.3
Treat with isotretinoin and register as female of nonchildbearing potential	12.1
Treat with isotretinoin and register as female of childbearing potential	76.6
Do not offer treatment with isotretinoin	0.9
Case 3: You determine that a 24-year-old transgender woman with acne would benefit from treatment with isotretinoin.	
At birth she was classified as male. She identifies as a heterosexual female and is in a monogamous relationship with a male. For gender dysphoria, she receives weekly intramuscular leuprolide injections and takes estradiol daily but has no plans for surgical procedures. She has legally changed her gender to female on her driver's license and in her medical record. How would you treat this patient?	
Treat with isotretinoin and register as male	42.1
Treat with isotretinoin and register as female of nonchildbearing potential	56.1
Do not offer treatment with isotretinoin	1.9

*Percentage answered out of the total number of surveys with the question answered. Questions that were skipped by participants were not included.

demographics, how they would enroll a transgender patient in iPLEDGE in 3 different case-based scenarios, 3 true or false questions regarding fertility in transgender patients receiving or after receiving hormonal therapy, and 6 questions regarding their attitudes and practice toward the prescription of isotretinoin in transgender patients.

Of the 136 respondents, the majority were women (60%) and attending physicians (61%). Nearly half (48.1%) were between the ages of 25 and 34 years. Our 3 case-based scenarios found no consensus on how to enroll transgender patients in iPLEDGE (Table I). However, 50% of respondents reported that they have encountered this issue in practice, and 11.8% admitted that the complexity of prescribing isotretinoin for transgender patients has led them to choose alternate therapies. As a solution, most respondents (89.4%) favored changing the iPLEDGE categories to gender-neutral options with an emphasis on pregnancy potential. Responses to knowledge true/false questions regarding the reproductive potential of transgender patients receiving or after receiving hormonal therapy were varied (Table II).

Our results show that this challenging scenario is being encountered in practice and that dermatologists are uncertain about how to proceed (Table I). They suggest that continued education on fertility in transgender patients is needed because prescribers must fully understand each patient's reproductive potential to safely prescribe teratogenic medications. The lack of consensus in our case-based scenarios highlights the confusion among practitioners regarding how to enroll transgender patients in iPLEDGE. Our results regarding current practice in prescription suggest a potential for systematic bias because respondents admitted that the complexity of this issue may discourage them from prescribing isotretinoin for transgender patients (Table II).

Table II. Responses to questions regarding knowledge, attitudes, and practice

Questions on knowledge (true/false)	Answered correctly, %*
Testosterone therapy decreases the quality and development of immature ovum.	28.8
Transgender males (female to male) can become pregnant after exposure to testosterone treatment.	89.6
Transgender females (male to female) may have normal spermatogenesis after long-term exposure to estrogen treatment.	82.4
Questions on attitude	**Answer, %***
Should the categories in the iPLEDGE program be changed to gender-neutral and classify patients by the ability to become pregnant?	
Yes	89.4
No	10.6
Do you have any reservations about changing the iPLEDGE program categories?	
Yes	12.5
No	87.5
If you selected *yes*, please expand upon what reservations you have:	
More complicated/confusing	92.3
More bureaucracy	7.7
Increased training	0
Increased time	0
Other	0
Questions on practice	**Answer, %***
Have you encountered this problem (of registering transgender patients in iPLEDGE) in your practice?	
Yes	50
No	50
If you selected *yes* to encountering this problem in your practice, do you think it has influenced you to choose alternate therapies?	
Yes	11.8
No	88.2
Would the complexity of this issue discourage you from prescribing this medication to a transgender patient?	
Yes	13.5
No	86.5

*Percentage answered out of the total number of surveys with the question answered. Questions that were skipped by participants were not included.

A major limitation is our small sample size (n = 136), which was skewed to younger women and was exclusively academic dermatologists. Without an evenly distributed population, the views reported in this survey may not reflect those of all dermatologists or be generalizable outside academic settings. There is also potential for selection bias, with possible oversampling of individuals interested in transgender health. Furthermore, our survey instrument was not validated, and not all participants completed the survey in its entirety.

Despite these limitations, our study suggests that the current iPLEDGE categories do not offer an inclusive approach to care for transgender patients. Moreover, it shows varied knowledge among prescribers regarding transgender patients' reproductive potential. The overwhelming majority of respondents were in favor of change to gender-neutral categorization that focuses on reproductive potential. These results align with current efforts at reform[5] of iPLEDGE to allow dermatologists to provide culturally competent care.

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Frequency of dramatic price increases for topical medications, 2014-2018

To the Editor: Topical medications are a ubiquitous treatment in dermatology. Although the average prices of generic topical medications have been declining, dramatic price increases have been identified as an issue affecting patient access to care.[1,2] The US Government Accountability Office has estimated that almost half of these increases have affected dermatologic drugs.[3] Decreased competition and supply shortages have been suggested as reasons for fluctuation, but little is known about whether the frequency of price increases is changing over time.[4]

To evaluate trends in dramatic price increases of more than 100% for topical medications, we performed cross-sectional and longitudinal analysis of National Average Drug Acquisition Cost data from the Medicaid Pharmacy Pricing database from January 1, 2014, through December 19, 2018. This data set is maintained by the Centers for Medicare and Medicaid Services (CMS) and accounts for manufacturer-to-pharmacy discounts, which provides a more accurate estimate of true drug costs. However, the National Average Drug Acquisition Cost data are not able to account for negotiations between drug manufacturers and pharmaceutical benefit managers.

The present study was deemed exempt from obtaining institutional review board approval by the University of Pennsylvania institutional review board because all data are publicly available and deidentified. Statistical analyses were performed with Stata/IC, version 14.2 (StataCorp, College Station, TX). The frequency of price increases of more than 100% was recorded and stratified by drug class, whether the medication was branded or generic, and reporting year. To account for differences in the number of medications in each drug class, we compared the mean number of price increases of more than 100% per medication in each category (Fig 1) and the magnitude of these price increases (Fig 2).

Drug classes (percentage of price reports) included topical corticosteroids (TCS) (28.6%), antifungals (19.8%), treatments for acne/rosacea (11.4%), antibiotics (7.0%), retinoids (7.0%), antineoplastics (4.1%), emollients (2.3%), calcineurin inhibitors (1.6%), antivirals (1.1%), antiparasitics (1.0%), and other miscellaneous medications (16.2%). Overall, 60.6% of price reports were for generic medications.

Overall among branded medications, TCS, antineoplastics, and retinoids accounted for the most frequent price increases per medication in each class (0.37, 0.13, and 0.08 during the study period, respectively). Among generics, antineoplastics, retinoids, and TCS had the most price increases (0.08, 0.08, and 0.06 increases per medication during the study period, respectively). Frequency of price increases was associated with drug class for branded and all medications (chi-square test, $P < .001$ for both) but not generic medications ($P = .54$). Moreover, for branded, generic, and all medications, frequency of price increases trended down from 2014 through 2018 (chi-square test for trend, $P = .002$, .021, and .002, respectively).

Among branded medications, antineoplastics showed the highest median price changes for a 30-g supply ($878.96), followed by antifungals ($128.66) and antibiotics ($114.95). For generics, the largest mean (interquartile range) price increases were among antineoplastics ($156.36 [$64.78-$195.30]), retinoids ($54.36 [$47.74-$56.14]), and TCS ($33.46 [$6.83-$71.18]).

These data suggest that dramatic price increases for topical medications are decreasing, although true prices are difficult to measure because of factors such as pharmacy benefit manager rebates to payers. This reduced frequency of price increases may be related to antitrust litigation by the US Department of Justice against collusion and scrutiny