Table I. Cont'd

Variable	OR (*P* value)	95% CI
Breslow depth, mm		
≤1.0	Reference	-
1.01-2.00	1.084 (<.001)	1.048-1.122
2.01-4.00	1.179 (<.001)	1.132-1.228
>4.00	1.421 (<.001)	1.357-1.487
No. positive nodes		
0	Reference	-
1	1.108 (.015)	1.020-1.203
2-3	1.238 (.001)	1.095-1.400
≥4	1.414 (<.001)	1.202-1.664

CI, Confidence interval; *Q*, quartile; *OR*, odds ratio.

States, have better access to care than smaller towns. It is possible that the larger patient populations in these areas makes prompt treatment of a diagnosed melanoma logistically more difficult. This is supported by our finding that patients treated at larger academic centers are more likely to experience delays. Together with our finding of increased delays for patients located farther from their treating facility, our study findings highlight a potential limitation of increasingly popular large regional centers of excellence for cancer care, namely that the patient volume of such centers might compromise their ability to provide timely care. Nevertheless, previous work has demonstrated that, in spite of these delays, such centers achieve improved patient survival outcomes.[8] It is not clear whether our findings of the impact of patient race and insurance status on the likelihood of delay reflect health differences or true care disparities.[9] Further study of the underlying causes of these regional and system-level variations in treatment delay might reveal approaches to better optimize melanoma care.

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Knowledge and opinions among Canadian academic physicians regarding genetic screening to prevent severe cutaneous adverse drug reactions

To the Editor: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare drug reactions with high mortality and long-term physical and psychological complications.[1,2] Carbamazepine and allopurinol are frequent inducers of SJS and TEN. Certain populations are genetically predisposed to SJS and TEN caused by carbamazepine and allopurinol: human leukocyte antigen B (*HLA-B*) *15:02-positive Asians taking carbamazepine and *HLA-B**58:01-positive Asians and Europeans taking allopurinol. *HLA-B**15:02 is not associated with SJS and TEN in the Japanese, Koreans, or Europeans, and the association between *HLA-B**58:01 and allopurinol-induced SJS and TEN has not been studied in populations other than Asians and Europeans.[3] In a study conducted in Taiwan, screening for *HLA-B**15:02 and avoidance of carbamazepine produced no cases of SJS and TEN compared with a historical incidence of 0.23%.[4] Similar findings were demonstrated for allopurinol-induced SJS and TEN.[5] International regulatory agencies and medical associations have recommended routine genetic

Table I. Participant responses to knowledge-related questions on genetic screening to prevent carbamazepine- and allopurinol-induced SJS and TEN

Drug, question [correct response]	No. participants answering correctly/total (%)*						
	Overall, n = 294	Dermatology, n = 28	Hematology, Nephrology, Oncology, and Rheumatology,† n = 37	Other Internal Medicine, n = 96	Neurology and Psychiatry,‡ n = 78	Other, n = 55	*P* value§
Carbamazepine							
Most common inducer of SJS and TEN listed [carbamazepine]	211/294 (72)	27/28 (96)	21/37 (57)	74/96 (77)	58/78 (74)	31/55 (56)	<.001
Ethnicities at highest risk of carbamazepine-induced SJS and TEN [Asian]	82/290 (28)	21/28 (75)	4/37 (11)	22/96 (23)	30/78 (39)	5/51 (10)	<.001
Genetic background strongly associated with carbamazepine-induced SJS and TEN [*HLA-B**15:02]	46/287 (16)	16/28 (57)	4/37 (11)	8/96 (8)	14/78 (18)	4/48 (8)	<.001
Aware of FDA recommendations¶ for genetic screening for *HLA-B**15:02 in Asian patients before carbamazepine use [yes]	52/286 (18)	16/28 (57)	3/37 (8)	9/96 (9)	21/78 (27)	3/47 (6)	<.001
Aware of clinical availability of genetic testing for *HLA-B**15:02 in Canada [yes]	75/285 (26)	16/28 (57)	6/37 (16)	22/96 (23)	22/78 (28)	9/46 (20)	.006
Allopurinol							
Most common inducer of SJS and TEN listed [allopurinol]	153/270 (57)	27/28 (96)	29/37 (78)	71/96 (74)	18/78 (23)	8/31 (26)	<.001
Ethnicities at highest risk of allopurinol-induced SJS and TEN [Asian and European]	21/267 (8)	8/28 (29)	2/37 (5)	6/96 (6)	4/78 (5)	1/28 (4)	<.001
Genetic background strongly associated with allopurinol-induced SJS and TEN [*HLA-B**58:01]	28/265 (11)	8/28 (29)	10/37 (27)	8/96 (8)	1/78 (1)	1/26 (4)	<.001
Aware of 2012 ACR guideline recommendations‖ for genetic screening for *HLA-B**58:01 in high-risk populations before allopurinol use [yes]	37/264 (14)	9/28 (32)	8/37 (22)	17/96 (18)	3/78 (4)	0/25 (0)	<.001
Aware of clinical availability of genetic testing for *HLA-B**58:01 in Canada [yes]	120/264 (45)	13/28 (46)	16/37 (43)	54/96 (56)	29/78 (37)	8/25 (32)	.18

ACR, American College of Rheumatology; *FDA*, Food and Drug Administration; *HLA-B*, human leukocyte antigen B; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

*Percentages might not sum to 100% due to uncategorized responses. Percentages calculated relative to number of respondents for each question.

†Specialties more likely to routinely prescribe allopurinol.

‡Specialties more likely to routinely prescribe carbamazepine.

§*P* values were calculated by using Chi-squared or Fisher's exact test comparing question responses across various physician specialties.

¶US FDA guidelines (2007) recommend genetic screening of patients of Asian ancestry for *HLA-B**15:02 before starting carbamazepine. *HLA-B**15:02-positive patients should not be treated with carbamazepine. This recommendation is based on data from Hung SI, Chung WH, Jee SH, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet Genomics*. 2006;16(4):297-306.

‖The ACR guidelines (2012) recommend the consideration of genetic screening of subpopulations at higher risk for severe allopurinol hypersensitivity syndrome (ie, Koreans with stage 3 or worse chronic kidney disease and all Han Chinese and Thai patients) for *HLA-B**58:01 before prescribing allopurinol. *HLA-B**58:01-positive patients should not be treated with allopurinol; febuxostat should be instead considered. This recommendation is based on data from Hung SI, Chung WH, Liou LB, et al. *HLA-B**5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci U S A*. 2005;102(11):4134-4139.

Table II. Participant responses to practice and opinion-related questions on genetic screening to prevent carbamazepine- and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis

Drug, question, response	No. participants responding/total (%)*						
	Overall, n = 294	Dermatology, n = 28	Hematology, NEphrology, ONcology, and RHeumatology,† n = 37	Other Internal Medicine, n = 96	Neurology and psychiatry,‡ n = 78	Other, n = 55	*P* value§
Carbamazepine							
Does or has ever prescribed, yes	152/291 (52)	2/28 (7)	6/37 (16)	50/93 (54)	67/78 (86)	27/55 (49)	<.001
Prescribing pattern							<.001
Regularly	19/151 (13)	0/2 (0)	0/6 (0)	0/50 (0)	18/67 (27)	1/26 (4)	
Rarely	130/151 (86)	2/2 (100)	6/6 (100)	50/50 (100)	47/67 (70)	25/26 (96)	
Refers patients for genetic screening before use							.43
Always or almost always	7/147 (5)	0/2 (0)	0/6 (0)	2/50 (4)	5/67 (7)	0/22 (0)	
Sometimes	8/147 (5)	1/2 (50)	0/6 (0)	2/50 (4)	5/67 (7)	1/22 (5)	
Never	100/147 (68)	1/2 (50)	2/6 (33)	37/50 (74)	45/67 (67)	15/22 (68)	
Other	32/147 (22)	0/2 (0)	4/6 (67)	9/50 (18)	12/67 (18)	6/22 (27)	
Finds it worthwhile to refer at-risk patients for genetic screening before use							.48
Strongly agree	89/145 (61)	1/2 (50)	5/6 (83)	29/50 (58)	43/67 (64)	11/20 (55)	
Agree	45/145 (31)	1/2 (50)	1/6 (17)	17/50 (34)	21/67 (31)	5/20 (25)	
Neutral	10/145 (7)	0/2 (0)	0/6 (0)	4/50 (8)	2/67 (3)	4/20 (20)	
Strongly disagree	1/145 (1)	0/2 (0)	0/6 (0)	0/50 (0)	1/67 (1)	0/20 (0)	
Allopurinol							
Does or has ever prescribed, yes	125/269 (46)	6/28 (21)	34/36 (94)	72/96 (75)	1/77 (1)	12/31 (39)	<.001
Prescribing pattern							<.001
Regularly	46/125 (37)	0/6 (0)	25/35 (74)	18/72 (25)	1/1 (100)	2/12 (17)	
Rarely	76/125 (61)	5/6 (83)	9/35 (26)	52/72 (72)	0/1 (0)	10/12 (83)	
Refers patients for genetic screening before use							.10
Always or almost always	5/124 (4)	2/6 (33)	1/34 (3)	2/72 (3)	0/1 (0)	0/11 (0)	
Sometimes	5/124 (4)	1/6 (17)	1/34 (3)	4/72 (6)	0/1 (0)	0/11 (0)	
Never	102/124 (82)	2/6 (33)	29/34 (85)	61/72 (85)	1/1 (100)	9/11 (82)	
Other	12/124 (10)	1/6 (17)	3/34 (9)	5/72 (7)	0/1 (0)	2/11 (18)	
Finds it worthwhile to refer at-risk patients for genetic screening before use							.02
Strongly agree	74/123 (60)	5/6 (83)	22/34 (65)	41/72 (57)	0/1 (0)	6/10 (60)	
Agree	38/123 (31)	1/6 (17)	8/34 (24)	28/72 (39)	0/1 (0)	1/10 (10)	
Neutral	10/123 (8)	0/6 (0)	4/34 (12)	3/72 (4)	1/1 (100)	2/10 (20)	
Strongly disagree	1/123 (1)	0/6 (0)	0/34 (0)	0/72 (0)	0/1 (0)	1/10 (10)	

*Percentages might not sum to 100% due to uncategorized responses. Percentages calculated relative to number of respondents for each question.
†Specialties more likely to routinely prescribe allopurinol.
‡Specialties more likely to routinely prescribe carbamazepine.
§*P* values were calculated using Chi-squared or Fisher's exact tests comparing question responses across various physician specialties.

screening before using these medications in at-risk populations.[3] We sought to assess the knowledge and clinical practices on this topic among Canadian academic physicians.

An anonymous online SurveyMonkey-based questionnaire was distributed to physicians affiliated with the Departments of Medicine, Psychiatry, and Family Medicine at the University of Toronto. Questions were on knowledge and medical practice regarding carbamazepine- and allopurinol-induced SJS and TEN (Tables I and II). Responses were collected during April and May 2018. The study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board. Chi-squared and Fisher's exact tests were used to compare the responses across 5 groups of physician specialties (R version 3.5.1).

From the 2188 invited physicians, 261 complete and 33 partial responses were returned. Participant responses to knowledge-related questions and practice and opinion-related questions are summarized in Tables I and II, respectively. Physicians were cognizant of carbamazepine and allopurinol as common inducers of SJS and TEN, but knowledge of the at-risk ethnicities and genetic associations was limited. Awareness of clinical availability of pertinent genetic screening and usage guidelines was generally low.

The educational component of our study successfully highlighted this topic's clinical importance. Almost all participants (~90%) agreed that genetic screening before prescribing these medications would be worthwhile. Furthermore, we received many responses regarding practical implementation of the knowledge provided. An internal medicine program director stated, "It's one of the few studies I've learned from! What's the route for testing? We have a large vulnerable Toronto population." An academic dermatologist replied, "This is my reality. We have a huge Asian population. I need to know more … and persuade rheumatologists and nephrologists to do the test." In Canada and the United States, testing for *HLA-B**15:02 and *HLA-B**58:01 can be ordered from academic centers and private laboratories. Turnaround times vary from 3 to 10 days. Costs are $150-300 USD/test and expected to decline.

Study limitations include a reliance on self-reported information, small cohort, and restricted population. Our study found a major knowledge gap between the validated literature on genetic screening to prevent SJS and TEN relative to the (lack of) clinical insight into this topic among Canadian academic physicians. Our results identify a need for health authorities to educate practitioners regarding pharmacogenetic screening to prevent SJS and TEN and ultimately, as done in some countries, to create a national screening program of personalized safe prescribing.

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Disclaimer: The findings and conclusions of this study are those of the authors and do not necessarily reflect the views of the Canadian Dermatology Foundation.

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Secukinumab demonstrates sustained efficacy in clearing skin and improving patient-reported outcomes in patients with moderate-to-severe psoriasis through 2 years of treatment: Results from the CLEAR study

To the Editor: Secukinumab is a fully human monoclonal antibody that selectively neutralizes interleukin 17A, a key cytokine involved in the development of psoriasis.[1] Secukinumab has shown long-lasting efficacy and safety in the complete spectrum of psoriatic disease, including disease localized to nails, scalp, palms and soles, and joints (peripheral and axial arthritis).[1-3] Given the chronic and relapsing nature of psoriasis, long-term data might help to fully characterize the efficacy and safety profile of secukinumab as well as its impact on quality of life.

The CLEAR study (NCT02074982) was a phase 3b, head-to-head, randomized, double-blind study on the efficacy and safety of secukinumab compared with ustekinumab over 52 weeks of treatment in adult patients with moderate-to-severe psoriasis. Results from the 16-week and 52-week time points showed higher and sustained superior efficacy of secukinumab versus ustekinumab; secukinumab use also provided a greater improvement in patient-reported outcomes (PROs), and its safety profile was comparable with ustekinumab.[4,5] Patients from the secukinumab arm who completed 52 weeks of treatment and consented to continue in the open-label extension phase received secukinumab 300 mg at week 52, followed by dosing every 4 weeks to week 100. Methods for the CLEAR study have been described in detail elsewhere.[4,5] Here, we present the efficacy, safety, and PROs from a total of 2 years of secukinumab treatment.

Of 337 patients randomized to receive secukinumab 300 mg, 312 completed the 52-week study, and 303 patients entered the extension phase. In total, 277 patients completed the 2-year extension study. Irrespective of the analysis (observed, multiple imputation, modified nonresponder imputation), Psoriasis Area and Severity Index 75, 90, and 100, and Investigator's Global Assessment 2011 modified version 0/1 response rates with secukinumab treatment at week 16 were sustained up to year 2 (Table I). A similar trend was seen for the Dermatology Life Quality Index 0/1 response. Further, the mean scores for patient assessment of psoriasis-related pain, itching, and scaling severity remained low up to year 2 of secukinumab treatment (Table I). Secukinumab treatment resulted in a mean percentage of change of −85.6% for pain, −77.6% for itching, and −81.9% for scaling from baseline to year 2. Furthermore, a high proportion of patients achieved complete relief (score 0) of psoriasis-related pain, itching, and scaling at week 16, and the response was sustained up to year 2 (Table I).

Among adverse events of interest, *Candida* infections were reported in 24 (7.2%) patients (all events were nonserious and did not lead to study discontinuation) and malignant or unspecified tumors were reported in 5 (1.5%) patients. Neutropenia was reported in 1 patient during the first year of treatment (mild severity, not associated with any infection or opportunistic infections). Overall, there was no increase in the rate of adverse events, and no new or unexpected signals were identified (Table II).

In conclusion, the 2-year results from the CLEAR study confirm the sustained efficacy and improved PROs provided by secukinumab in patients with