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High-Risk Cutaneous Squamous Cell Carcinoma: A Review for Dermatologists on Definition, Risk Factors, Clinical Staging, and Management

Robert Bobotsis, MD, MSc SLI, FRCPC, DABD, FACMS

Cutaneous squamous cell carcinoma (cSCC) is a common cutaneous malignancy with an increasing incidence that is highly treatable with excellent outcomes in most cases. The goal of this review is to arm the dermatologist with the broad clinical information needed to identify and/or appropriately treat the smaller subset of cSCCs that are high risk and contribute to disease specific morbidity and mortality. Key topics include defining high-risk Squamous cell carcinoma (SCC) risk factors, staging, lymph node assessment, and management strategies. Management of mucosal, locally advanced, and metastatic SCC are beyond the scope of this review.

Introduction

Squamous cell carcinoma (SCC) is the second most common cutaneous malignancy, accounting for approximately 20% of skin cancers, and its incidence continues to rise.[1,2] Fortunately, the vast majority of cutaneous SCC (cSCC) cases are associated with an excellent prognosis (>90% 5-year overall survival).[2] However, a small subset of cSCCs progress to locally advanced disease—defined as no longer readily amenable to surgery and/or radiation with curative intent—and have the potential for metastasis, causing significant morbidity and mortality.[1,2] Although cSCC accounts for approximately 20% of skin cancer deaths, given the large number of cases, the absolute number of deaths is comparable to that observed with melanoma.[3]

Definition of High-Risk SCC

While there is no agreed upon definition, high-risk cSCCs have at least one high-risk feature (often more than one), tend to recur, and/or progress to an advanced stage of disease that includes locally advanced tumours, regional spread to lymph nodes, or metastatic disease.[3] These cases are often inoperable or difficult to treat, requiring systemic therapy.[3] Given the large number of cSCC cases each year, accurate identification of high-risk lesions is of utmost importance. Distinguishing the minority of cSCCs that are high-risk can be clinically challenging; however, timely recognition, appropriate treatment, and referral by dermatologists are essential to prevent high-risk SCC from progressing to locally advanced or metastatic disease.

High-Risk SCC Risk Factors and Staging Systems

Multiple reported tumour characteristics, patient factors, and histologic features have been associated with high-risk SCC due to their association with poorer outcomes, including increased risks of local recurrence, spread to lymph nodes, distant metastasis, and death. The presence of more than one high-risk feature is thought to portend a worse outcome.

Several international cSCC staging systems incorporate high-risk features in their criteria, with the most widely used being the American Joint Committee on Cancer 8th edition (AJCC8) and the Brigham Women's Hospital (BWH) systems. Both AJCC8 and BWH incorporate high-risk factors into tumour (T) classifications (**Table 1**). However, there is overall less evidence validating the clinical outcomes of AJCC8, whereas the BWH system appears to offer superior prognostication, although it is limited by data derived from a single academic institution.[4,5]

In contrast to staging systems, which provide prognostic information, several published guidelines have been developed on diagnosis and management of cSCC, including those from the American Academy of Dermatology (AAD), the National Comprehensive Cancer Network (NCCN), and the American Society for Radiation Oncology (ASTRO). Among these, the 2022 NCCN guidelines are widely used and stratify cSCC into low-risk, high-risk, and very high-risk categories, requiring the presence of at least one risk factor to qualify for a risk category.[6]

High-risk features include tumour size (diameter >2 cm in AJCC8 and BWH systems, with further subcategorization based on anatomic site (NCCN criteria—see **Table 2**), tumour thickness (>2 mm per NCCN versus >6 mm and/or invasion beyond subcutaneous fat in AJCC8 and BWH), rapidly growing tumours, ill defined borders, and high-risk anatomic locations (e.g., lips/ears). Additional factors include poor differentiation and other rare histologic subtypes (desmoplastic, acantholytic, adenosquamous), perineural invasion (wherein symptomatic perineural invasion [PNI] portends a worse prognosis than incidental/histologic PNI), lymphovasculation invasion, chronic inflammation/wounds, and recurrent tumours (see **Tables 1 and 2**).

Several studies have attempted to quantify the relative risk of metastasis associated with high-risk factors. In a large meta-analysis of 36 retrospective and prospective cohort studies comprising 17,248 patients, Thompson et al., identified the following risk factors as significantly

AJCC8 and BWH T staging systems	
AJCC 8th Edition	
T1	<2 cm in greatest diameter
T2	≥2 cm but <4 cm in greatest diameter
T3	Tumour ≥4 cm in greatest diameter or minor bone invasion or perineural invasion or deep invasion[a]
T4a	Tumour with gross cortical bone and/or marrow invasion
T4b	Tumour with skull bone invasion and/or skull base foramen involvement
BWH	
T1	0 high-risk factors[b]
T2a	1 high-risk factors
T2b	2–3 high-risk factors
T3	4 high-risk factors or bone invasion

Table 1. Most widely used cutaneous squamous cell carcinoma staging systems[1]; *adapted from Guzman AK, Schmults CD, Ruiz CS. Squamous Cell Carcinoma: An Update in Staging, Management and Postoperative Surveillance Strategies. Dermatol Clinics. 2023;41(1):1-11. doi:10.1016/j.det.2022.07.004*

[a] Deep invasion defined as invasion beyond the subcutaneous far or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumour), perineural invasion defined as tumour cells in the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.

[b] BWH high-risk factors include tumour diameter 22 cm, poorly differentiated histology, perineural invasion of nerves 20.1 mm in caliber, or tumour invasion beyond subcutaneous fat (excluding bone invasion, which upgrades tumour to BWH stage T3).

associated with metastasis: tumour size >20 mm, thickness >6 mm, poor differentiation, PNI, extension beyond the subcutaneous fat, involvement of high-risk anatomical sites (lip, ear, and temporal region), and immunosuppression (**Table 3** summarizes additional smaller studies).[7,8]

Because most cSCCs with high-risk features do not progress, the ability of staging systems to predict which tumours will develop locoregional spread, metastasis, or disease specific death remains low.[2] The positive predictive value of AJCC8 is only 17% while the BWH staging system performs only slightly better, with a positive predictive value for poor outcomes of 24–38%.[2]

Lymph Node Assessment

Aggressive cSCC follows a stepwise progression, first to regional lymph nodes before the development of distant metastases. Large cohort studies from Australia suggest the risk of spread to lymph nodes among cSCC patients is approximately 5% over 5 years.[5] Despite its small sample size (459 patients with 680 head and neck cSCCs), the BWH staging system is the only system that has specifically evaluated the risk of lymph node mestastasis, demonstrating an overall risk of positive sentinel lymph node biopsy (SLNB) of 34.7% among patients with T2b/T3 tumours.[5] Additionally, small retrospective studies have demonstrated up to a 92% 5-year survival rate for patients with one small positive node (<3 cm without extracapsular spread), suggesting that early diagnosis could improve patient outcomes.[5] However, while all patients with cSCC should undergo a thorough clinical assessment of draining lymph node basins, there are currently no guidelines specifying which cSCCs should undergo imaging before or after treatment. Similarly, due to insufficient data, there are no established criteria to guide the selection of patients with cSCCs for SLNB.

NCCN Risk Stratification[a]			
Characteristic	NCCN risk group		
	Low	High	Very high
History and physical			
Location and size	Trunk, extremities <2 cm	Trunk, extremities 2 to <4 cm; head, neck, hands, feet, pretibial, and anogenital (any size)	≥4 cm (any location)
Borders	Well-defined	Poorly defined	N/A
Primary vs recurrent	Primary	Recurrent	NA
Immunosuppression	Negative	Positive	N/A
Site of prior RT or chronic inflammatory process	Negative	Positive	N/A
Rapidly growing tumour	Negative	Positive	N/A
Neurological symptoms	Negative	Positive	N/A
Pathological findings			
Degree of differentiation	Well or moderately differentiated	N/A	Poor differentiation
Histologic features: acantholytic (adenoid), adenosquamous (showing mucin production), or metaplastic (carcinosarco- matous) subtypes	Negative	Positive	Desmoplastic SCC
Depth: thickness or level of invasion	≤6 mm and no invasion beyond subcutaneous fat	N/A	>6 mm or invasion beyond subcutaneous fat
Perineural involvement	Negative	Positive	Tumour cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1 mm
Lymphatic or vascular involvement	Negative	Negative	Positive

Table 2. In 2022, the National Comprehensive Cancer Network (NCCN) revised its classification of risk factors, expanding from the previous low-risk and high-risk categories to three categories: low-risk, high-risk and higher-risk; however, this updated classification has not been clinically validated[6]; *courtesy of Stevens JS, Murad F, Smile TD, O'Connor DM, Ilori E, Koyfman S, et al. Validation of the 2022 National Comprehensive Cancer Network Risk Stratification for Cutaneous Squamous Cell Carcinoma. JAMA Dermatol. 2023159(7):728-735. doi:10.1001/jamadermatol.2023.1353*

Abbreviations: NA: not applicable; **NCCN:** National Comprehensive Cancer Network; **RT:** radiotherapy; **SCC:** squamous cell carcinoma.

[a] Adapted from NCCN 2022 guidelines. Any tumour with 1 or more high- or very high-risk features was categorized as high risk or very high risk, respectively.

Risk, hazard, or odds ratios for high-risk features of cutaneous SCC with independent risk of metastasis from different studies.				
High-risk features	**Papers (*n* = number of patients) HR or OR (95% confidence interval), *p* value***			
	Thompson et al.[11] (*n* = 17248), RR	**Moore et al.[6] (*n* = 193) OR**	**Peat et al.[12] (*n* = 170) HR**	**Mourouzis et al.[13] (*n* = 194) OR**
Tumour size ≥20 mm	6.15 (3.56–10.65), *p* < 0.01		–	
Depth of invasion	10.76† (2.55–45.31), *p* < 0.01	–	–	
	6.93‡ (4.02–11.94), *p* < 0.01			
	11.21§ (3.59–34.97), *p* < 0.01			
Recurrent lesion			2.81 (1.28-6.17), *p* < 0.01	
Poor differentiation	4.98 (3.30–7.49), *p* < 0.01		–	–
Perineural invasion	2.95 (2.31–3.75), *p* < 0.01		4.53 (1.43-14.30), *p* < 0.01‖	
Lymphovascular invasion		7.54 (2.52-22.6), *p* < 0.0001	4.53 (1.43-14.30), *p* < 0.01‖	
Temple	2.82 (1.72–4.63), *p* < 0.01			
Cheek	1.30 (0.61–2.77), *p* = 0.49			
Ear/auricular area	2.33 (1.67–3.23), *p* < 0.01			–
Lip	2.28 (1.54–3.37), *p* < 0.01			
Immunosuppression	1.59 (1.07–2.37), *p* = 0.02			
Incomplete excision				2.00, (1.00–4.00), *p* = 0.05

Table 3. Relative risk of metastasis due to high-risk features. Data analyzed retrospectively[8]; *courtesy of Skulsky SL, O'Sullivan B, McArdle O, Leader M, Roche M, Conlon PJ, O'Neill JP. Review of high-risk features of cutaneous squamous cell carcinoma and discrepancies between the American Joint Committee on Cancer and NCCN Clinical Practice Guidelines In Oncology. Head Neck. 2017;39(3):578-594. doi:10.1002/hed.24580*

Study addressing the risk factor is used in Thompson et al.'s meta-analysis, blank cell means risk factor was not examined/reported.

*HR or OR listed, as given by original article
†Breslow thickness >2 mm
‡Breslow thickness >6mm
§For depth beyond subcutaneous fat
‖Combined

Abbreviations: HR: hazard ratio, **OR:** odds ratio, **RR:** risk ratio

Despite the limited evidence base, NCCN guidelines suggest considering SLNB in patients with recurrent SCC or SCCs with multiple risk factors, while the European consensus-based interdisciplinary guideline recommends ultrasonography (US) for all patients with high-risk cSCC.[9,10] The optimal imaging modality remains unclear; however, limited retrospective data suggests that US may offer higher sensitivity and specificity for detecting nodal disease compared with computed tomography or magnetic resonance imaging, although performance is highly operator dependent.[5]

In a large systematic review, 1143 patients with high-risk cSCC who underwent SLNB were identified.[7] Among these, 88.1% had cSCC on the head and neck region, and the overall SLNB positivity rate was 12.3% (141/1143).[7] Of note, there was heterogeneity in how the high-risk SCC inclusion criteria were defined between studies, including the use of NCCN, AJCC, and BWH criteria.[7] Despite these differences, the rate of SLNB positivity exceeded 10% across studies, which is higher than the complication rate of approximately 5%, suggesting potential benefit.[7] However, no controlled studies have demonstrated a survival benefit for SLNB in cSCC.

Adjuvant Radiation Therapy

Radiation therapy is usually not recommended as a primary treatment modality in surgically resectable high-risk cSCC, except in cases where it is used for palliation, based on patient preference, or when surgery would result in significant disfigurement or morbidity. Evidence supporting the use of adjuvant radiation therapy post-resection of high-risk SCC is largely derived from retrospective and small sample size studies.[11] In a multidisciplinary context, adjuvant radiation therapy may be offered for select cases of high-risk SCC, including completely excised high-risk tumours, those with positive margins, tumours exhibiting PNI, and following lymph node dissection in the setting of regional spread.[11] The NCCN guidelines recommend adjuvant radiation following complete surgical excision in cases of PNI (**Table 4**).

Management of High-Risk SCC

Management of high-risk cSCC often involves a multidisciplinary team, including dermatologists, dermatologic surgeons, plastic surgeons or ear nose throat surgeons, radiation oncologists, and medical oncologists. Surgical resection should achieve complete circumferential and peripheral deep margin assessment, most commonly with the use of Mohs Micrographic Surgery, in which the dermatologist serves as both surgeon and pathologist, examining frozen sections in an en face orientation to achieve tumour extirpation. Depending on identified high-risk features, patients may subsequently undergo imaging of the lymph node basin and potential SLNB. These findings can inform further management decisions, including the use of radiation therapy, lymph node dissection, and, in some cases, immunotherapy as part of multidisciplinary care.

Discussion

cSCC *in situ* can be managed with a range of options, including electrodessication and curettage, topical agents (e.g., 5-fluorouracil, calcipotriene, imiquimod), cryotherapy, and/or photodynamic therapy.[10] The vast majority of invasive cSCCs are amenable to treatment with wide local excision or Mohs Micrographic Surgery. However, there is a small proportion of cases that warrant consideration of adjuvant treatment, imaging, and multidisciplinary care. As most cSCCs occur on the head and neck region (approximately 80%),[1,2] most will be treated with Mohs Micrographic Surgery to preserve healthy tissue in anatomically sensitive areas while ensuring clear margins prior to reconstruction, adjuvant therapy, or additional diagnostic evaluation if needed.

Gene expression profiles (GEP), while not routinely used in Canada, are clinically available. These tools have been designed to predict the risk of metastasis as low, moderate, or high, and are intended to guide further clinical decision making.[11] The 40-GEP, known as DecisionDx, evaluates 34 prognostic genes and six control genes to estimate the risk of metastasis, with class 1 having the lowest risk, and classes 2a and 2b indicating progressively higher risk.[10] Small studies are

Treatment	NCCN[7,78]	AAD[79]	ASTRO Task Force[40]
Radiation therapy	**Recommends ART to primary site[a]:** • for extensive PNI • with large (nerve caliber ≥0.1 mm) nerve involvement • when there are positive margins postsurgery	**Recommends consideration of ART to primary site:** • for concerning PNI • for high risk for regional or distant metastasis	**Strongly recommends ART to primary site:** • for clinically or radiologically apparent gross PNI • when further surgery cannot correct or close positive margins • when there is recurrence following a margin-negative resection • for T3 and T4 tumors (AJCC8) • for chronically immunosuppressed patients with desmoplastic or infiltrative tumours

Table 4. Recommendations for adjuvant radiation following cutaneous squamous cell carcinoma resection[11]; *courtesy of Newman JG, Hall MA, Kurley SJ, Cook RW, Farberg AS, Geiger JL, et al. Adjuvant Therapy for High-risk Cutaneous Squamous Cell Carcinoma:10-year Review. Head Neck. 2021;43(9):2822-2843. doi:10.1002/hed.26767*

exploring the use of these tools to predict which SCCs would benefit from adjuvant radiation following resection. However, widespread use remains limited by proof of clinical utility and the burden of payer coverage.

Post treatment follow up of cSCC is important for identifying tumour recurrence, regional spread, and screening for new keratinocyte carcinomas.[12] A recent systematic review by Canadian dermatologists, which evaluated 13 different keratinocyte guidelines, found a lack of consensus on follow up frequency and duration.[12] There was also a considerable lack of consensus in how high- versus low-risk cancer was defined.[8] The clinical utility of frequent follow up in immunocompetent patients remains unclear due to limited data, and does not account for healthcare resource constraints, given the low dermatologist-to-population ratio in Canada (1.24 dermatologists per 100,000 people).[12] Nonetheless, in addition to emphasizing the importance of strict sun protection during follow up assessments, dermatologists should also consider prescribing preventive treatments for high-risk SCC patients, including acitretin, niacinamide, and 5-fluorouracil.[2]

Conclusions

High-risk cSCC is associated with significant morbidity and mortality. Patient outcomes can be improved by early identification of high-risk features, prompt treatment to achieve clear surgical margins, identifying the earliest signs of recurrence, and timely referral for cases that would benefit from adjuvant radiation therapy. Further research is required to better define individual and combined risk factors that are predictive of lymph node metastasis, as well as to identify which patients are most likely to benefit from imaging and SLNB.

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Treatment of Psoriasiform Drug Eruptions in Patients on Immune Checkpoint Inhibitors

Nicola Gray, MD, FRCPC

Introduction

Immune checkpoint inhibitors are increasingly used in oncology, including in Canada.[1] Pembrolizumab alone is Health Canada-approved for at least 15 distinct cancer types.[2] Cutaneous immune-related adverse events (irAEs) are the most common toxicities associated with immune checkpoint inhibitors, occurring in more than 30% of patients. These reactions impair quality of life and can lead to temporary interruption or permanent cessation of these potentially lifesaving therapies.[3] With their increasing use, dermatologists in community practice, not only those in tertiary centres, are likely to encounter affected patients, and are well placed to improve both quality of life and treatment outcomes. The goal of this article is to review practical, community-based management strategies, with a focus on systemic therapy selection and oncologic safety.

Cutaneous irAEs comprise a wide range of clinical presentations, including maculopapular rash, pruritus, blistering disorders, lichenoid diseases, psoriasiform diseases, inflammation of the oral mucosa, and sicca syndrome/oral dysesthesia. Psoriasiform diseases account for approximately 23% of cutaneous irAEs, and are most strongly associated with programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) inhibitor monotherapy.[4,5] Notably, psoriasiform irAEs are unique in that systemic steroids are not part of the latest National Comprehensive Cancer Network (NCCN) treatment algorithm, given concerns about the risk of pustular rebound flares.[6] In clinical practice, patients with moderate-to-severe disease are referred to dermatology for assistance with non-steroid systemic treatments.

Brief Review of Pathogenesis and Clinical Features

Psoriasis is a complex immune-mediated disorder, driven by T cells and increased interleukin (IL)-23/Th17 signalling. The mechanism in the setting of immune checkpoint inhibitor therapy remains incompletely understood.[7] Psoriasiform irAEs include both de novo psoriasis, typically occurring within the first 5 to 12 weeks of therapy, and flares of pre-existing psoriasis, which tend to occur earlier in the treatment course.[7] Clinical findings mirror those of idiopathic psoriasis, including, but not limited to, plaque, guttate, inverse, palmoplantar, and pustular subtypes.[4,8-11] In one retrospective case series of 115 patients with immune checkpoint-mediated psoriasis, nail psoriasis occurred in 32.7% of cases, and psoriatic arthritis in 8.1%.[11] Skin biopsy findings are also consistent with idiopathic psoriasis, typically demonstrating a thickened stratum corneum with parakeratosis, psoriasiform epidermal hyperplasia, and a lymphocytic infiltrate.[4]

Treatment Principles

The aims of treatment are to achieve control of skin disease, thereby improving quality of life and avoiding interruption of immunotherapy where possible. Treatment is stratified according to the severity of the psoriasiform eruption. The most recent NCCN guidelines on the management of immune checkpoint inhibitor-related toxicities define psoriasis and psoriasiform disorders as mild if body surface area (BSA) <10%, moderate if BSA is 10–30% or when disease is not responsive to high-potency topical steroids, and severe if BSA is >30%.[6]

Mild Disease

Fortunately, most cases (85.9%) of psoriasiform irAEs are mild and can be managed with topical therapies, most commonly ultrapotent topical corticosteroids. In our setting, a topical combination gel or ointment containing calcipotriol 50 mcg/g and betamethasone dipropionate 0.5mg/g is most often used. For facial, inverse, or genital involvement, lower-potency topical steroids, or off-label tacrolimus 0.1% ointment are used. Alternative options include topical calcipotriol monotherapy, as well as newer on-label agents, such as topical roflumilast 0.3% or topical tapinarof 1%. In clinical practice, topical treatment selection is additionally influenced by costs and availability through provincial drug formulary listings.

Moderate and Severe Disease

The decision to interrupt potentially lifesaving immunotherapy is not clear-cut, particularly regarding moderate disease. NCCN guidelines recommend holding immunotherapy in moderate disease, whereas others recommend continuing immunotherapy with concurrent dermatologic consultation.[4,6] Management requires multidisciplinary decision-making involving the oncologist, dermatologist, and patient. Patient preferences for symptom control versus maintenance of immunotherapy should be carefully considered. For severe disease, guidelines unanimously recommend that therapy should be withheld.

Treatment options beyond topical therapies include narrowband ultraviolet B (UVB) phototherapy, if available and practicable for the patient. Systemic therapies include acitretin, apremilast, traditional immunomodulators such as methotrexate and cyclosporine, and biologic therapies.[4,6]

Acitretin and apremilast demonstrate relatively modest efficacy but are useful components of the psoriasis treatment toolkit as they are not immunosuppressive. Acitretin is useful for hyperkeratotic palmoplantar disease, and can be used in combination with phototherapy, although it lacks efficacy for treating psoriatic arthritis.[12] By contrast, apremilast can be used for psoriatic arthritis. The potential for phosphodiesterase-4 inhibitor-associated diarrhea needs to be kept in mind for patients started on apremilast (and to some extent, topical roflumilast), to avoid

confusion with symptoms of immune checkpoint inhibitor-induced colitis. In our setting, these agents are infrequently used, as we find alternative systemic agents are more effective.

There is concern that immunosuppressive treatments may reduce the efficacy of immune checkpoint inhibitors, with limited data available to assess this risk. This issue is of particular concern for cyclosporine, despite its inclusion in the NCCN guidelines as a potential treatment option for severe psoriasiform irAEs.[7,13] Specifically, cyclosporine downregulates CD8+ T-cell activation, while immune checkpoint inhibitors aim to promote CD8+ tumour reactive T-cell responses.[13] Real-world data evaluating the impact of cyclosporine on immune checkpoint inhibitor survival outcomes are lacking. Moreover, such studies addressing this question may not be ethical to pursue given the availability of alternative systemic immunomodulators, including more cost-effective options (methotrexate) and more targeted options with less global immunosuppression (biologics).

The Role of Biologics

Biologic agents approved for treating psoriasis, such as tumour necrosis factor (TNF), IL-17, and IL-23 inhibitors, are recommended for moderate-to-severe psoriasiform irAEs.[6] While TNF inhibitors demonstrate lower efficacy for psoriasis compared with other approved biologics, they may be appropriate in select cases, such as those with concomitant psoriatic axial spondyloarthritis or multi-system toxicity. It is reassuring to note that, despite their relatively upstream immunosuppressive effects, TNF inhibitors have been studied in the management of immune checkpoint inhibitor-associated colitis, with no association found between TNF inhibitor use and adverse disease outcomes.[14,15]

IL-17 inhibitors are an attractive option, particularly in cases where disease severity requires immune checkpoint inhibitor interruption, given their rapid response rates. In a network meta-analysis, the time for 50% of patients to achieve Psoriasis Area and Severity Index (PASI)75 is 3.4 weeks for bimekizumab, compared to 5.7 weeks for risankizumab, and 11 weeks for methotrexate.[16] Interestingly, IL-17 may play a role in immune checkpoint inhibitor resistance; accordingly, IL-17 inhibitors in combination with anti-PD-1 therapy are being studied for the treatment of microsatellite-stable colorectal cancers.[17] When considering IL-17 inhibition, the risk of inflammatory bowel disease needs to be considered and differentiated from immune checkpoint inhibitor-related colitis. In addition, patients need to be monitored for mucocutaneous candidiasis, particularly if they are receiving other chemotherapies that increase risk.

IL-23 inhibitors are highly effective, demonstrate a reasonably rapid onset, and have an excellent safety profile. Retrospective data shows no increased risk of cancer recurrence, progression, or development in patients with a history of cancer treated with IL-23i.[18] Furthermore, a 2025 Delphi consensus consisting of 15 specialists across multiple disciplines rated IL-23 inhibitors and systemic retinoids most favourably in terms of risk of impairing immune checkpoint inhibitor efficacy.[7]

Knowledge Gaps and Future Directions

The glaring gap in the literature is the lack of direct real-world evidence assessing whether immunosuppressive psoriasis treatments, particularly methotrexate, cyclosporine, and biologics, impact tumour response, progression-free survival, and overall survival. The development of registries and prospective cohort studies would be immensely helpful in this regard.

Furthermore, the relative efficacy and rate of onset of disease control is extrapolated from studies of idiopathic psoriasis; validation of these outcomes in the setting of immune checkpoint inhibitor-related disease would be highly informative.

Lastly, a better understanding of the pathogenesis of psoriasis as distinct from other cutaneous irAEs could help develop biomarkers to predict which patients are at highest risk of these reactions. Such biomarkers could assist with pre-emptive referral to dermatology and closer disease monitoring, allowing earlier detection

and treatment, and reducing the risk of treatment interruption. Implementing this approach would require close collaboration between oncology and dermatology, as well as measures to address long wait times for dermatology services. Other factors relevant in the Canadian setting include differences in provincial criteria for biologic access across provinces, and travel burden associated with accessing specialist care.

Conclusion

Psoriasiform eruptions are a relatively common and clinically distinct subset of cutaneous irAEs and are increasingly encountered in community dermatology practice. While mild disease can be managed with topical therapies, moderate and severe disease requires phototherapy and/or systemic agents. We are fortunate to have a broad range of systemic treatment options, including acitretin, apremilast, traditional immunosuppressants, and biologic therapies. However, in clinical practice, treatment options need to balance effective psoriasis control with preservation of anti-tumour immunity. In the absence of high-quality data, a patient-centred multidisciplinary approach is recommended to optimize quality of life and treatment outcomes.

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American Academy of Dermatology 2026—Highlights with a Pediatric Dermatology Focus

Cathryn Sibbald, MD

The 2026 annual meeting of the American Academy of Dermatology (AAD) was held in Denver, Colorado, from March 27–31. As expected, the meeting featured the presentation of new data and generated ongoing excitement about therapies and approaches aimed at optimizing our care of patients. This article summarizes several key takeaways, with a focus on those relevant to pediatric dermatology.

Atopic Dermatitis

Eric Simpson presented results from the COAST1, COAST2, and SHORE studies,[1,2] which investigated amlitelimab, a non-T-cell-depleting anti-OX40L antibody that blocks OX40L–OX40 interactions on activated T-cells. Dosing every 12 weeks demonstrated efficacy comparable to dosing every 4 weeks, with minimal adverse effects (**Table 1**). In the SHORE study, background topical corticosteroids or calcineurin inhibitors were allowed, which resulted in a 7–8% improvement across most measures at 24 weeks compared to outcomes observed in the COAST studies. Notably, discussion addressed the potential associated between OX40-targeted therapies and the risk of Kaposi's Sarcoma (KS), which has been linked to OX40 deficiency.[3] Further studies on rocatinlimab, a T-cell depleting OX-40 antibody, were put on hold recently due to several cases of KS reported in studies. Nevertheless, there may still be a role for targeting OX40 in select patients given its potential impact on memory T cells, especially for those recalcitrant or unable to receive other treatments. More data and research is clearly warranted, with consideration of potential baseline assessment and monitoring of serologic markers, as well as potential stratification by factors associated with higher incidence of KS (e.g., individuals from the

Netherlands or Turkey, men who have sex with men, and black Americans).[4]

Data were also presented for nemolizumab, a monoclonal antibody targeting interleukin (IL)-31, in children aged 2–11 years with atopic dermatitis (AD) (**Table 1**). After 16 weeks, clear or almost clear skin was achieved in 40.5–47.2% of patients. Rates of asthma (2.7%) and conjunctivitis (3.7%) were low. In addition to longer dosing intervals of 4 weeks in patients aged 6–11 years, which is not currently on-label for dupilumab in this age group, many providers have noted that the injections are well tolerated, with minimal associated pain. In a session focused on pruritus, Dr. Brian Kim shared his experience with new-onset cutaneous eruptions in patients receiving nemolizumab. He suggested that these eruptions could result from activation of the oncostatin M receptor beta (OSMR-B) receptor, which normally dimerizes with the IL-31 receptor. When the IL-31 receptor is blocked, the OSMR-B receptor is freed and can be activated, resulting in pro-inflammatory effects. In his clinical experience, these new-onset skin rashes were non-pruritic and either self-limited or responsive to topical medications.

Additional promising data in adults with AD were presented for several emerging systemic therapies, including MG-K10, a long-acting monoclonal antibody binding IL-4Rα, and blocking IL-4 and IL-13 signalling; zumilokibart, an extended half-life monoclonal antibody targeting IL-13, with dosing every 3 or 6 months; and KT-621, an oral signal transducer and activator of transcription 6 (STAT6) degrader that inhibits IL4 and 13, and is administered once daily.

With our growing armamentarium of topicals for pediatric AD, new data were presented for roflumilast 0.05% cream, applied once daily for infants aged 3 to 24 months. Results for the INTEGUMENT-INFANT study were presented by Dr Larry Eichenfield.[5] This phase 2 open label trial enrolled infants with mild to moderate AD, with 49% of participants achieving clear or almost clear scores at 4 weeks (**Table 1**). Dr. Eichenfield highlighted the high efficacy in scalp dermatitis and quick onset of itch relief (within hours).

Psoriasis

Considerable excitement surrounded the results of the Together-PsA study, presented by Dr. Merola during the late-breaking sessions, and recently published.[6] In this phase 3 study, adult patients with psoriatic arthritis, a body mass index (BMI) >39, and one obesity-related complication were randomized to receive ixekizumab alone or in combination with tirzepatide. At week 36, a greater proportion of patients in the combination group achieved an ACR50 response compared to those in the monotherapy group (33.5% vs 20.4%, $p<0.05$). A similar study conducted in adult patients with plaque psoriasis demonstrated superior Psoriasis Area and Severity Index responses with the combination approach, although these results have not yet been published. Dr. Merola noted that treatment differences appeared before weight loss, suggesting that the benefit of tirzepatide could be a result of anti-inflammatory effects in addition to weight changes. Although these studies were conducted in adult populations, it is notable that ixekizumab is approved in Canada for pediatric plaque psoriasis in children aged 6 years and older, and that other glucagon-like peptide-1 (GLP-1) receptor agonists (semaglutide and liraglutide) are approved for adolescents (12 years and older) with a BMI above the 95th percentile.

Equally exciting was the presentation and review of a new joint statement from the National Psoriasis Foundation and International Psoriasis council on tuberculosis (TB) screening, which advises that routine TB testing before and during treatment with IL-17 and IL-23 inhibitors is not required.[7] In his session dedicated to psoriasis, Dr. Anthony Fernandez reviewed the evidence underpinning these recommendations, emphasizing extensive and reassuring real-world data, including only a single reported case of latent TB reactivating in a patient receiving IL-17 inhibitors among hundreds of patients treated with IL-17 inhibitors and no reported cases of disseminated or extrapulmonary TB. Of note, this recommendation suggests screening could be continued for patients on concomitant immunosuppressive therapy and for those living in TB endemic areas.

Intervention	Population	Protocol	Results	Adverse Effects
Amlitelimab SC **Anti-OX40 Ligand Antibody**	**Patients with AD ≥12 years** **IGA: 3 or 4** **BSA: 10%+** **EASI: 16+** **NNRS**	COAST1+2 Randomized 2:1:1 • amlitelimab SC Q4W + LD • amlitelimab SC Q12W + LD • placebo 24 weeks	**COAST-1:** 24 weeks **vIGA-AD:** 0/1 Q4W: 21.1%, Q12W: 22.5% vs placebo: 9.2%; P < 0.01 **EASI-75:** 35.9%, 39.1% vs 19.1%; P < 0.001 **PP-NRS:** ≥4 22.5%, 24.5% vs 12.7%; P ≤ 0.02 **COAST-2:** N=589 **vIGA-AD:** 0/1: Q4W: 25.3%, Q12W: 25.7% vs **placebo:** 14.8%; P ≤ 0.025. **EASI-75:** 41.8%, 40.5% vs 24.2% **PP-NRS:** ≥4 26.8%, 27.2% vs 17.1%	**NP:** (7.3% vs 10.5%) **dermatitis:** (7.3% vs 22.4%) **URTI:** (5.3% vs 8.6%) **NP:** (5.9% vs 7.4%) **dermatitis:** (5.3% vs 2.7%) **URTI:** (4.8% vs 4.0%)
		SHORE: As per COAST but with background topical steroid or calcineurin inhibitor	**vIGA-AD:** 0/1 Q4W: 28.7%, Q12W: 32.3% vs placebo: 16.8%; P ≤ 0.01, **EASI-75:** 48.1%, 46.8% vs 32.3%; P ≤ 0.025 **PP-NRS≥4:** 38.2%, 33.3% vs 21.5%; P ≤ 0.025	**NP:** (9.5% vs 12.5%) **URTI:** (7.9% vs 4.4%) **dermatitis:** (2.7% vs 5.6%)
Rademikibart **Antibody to IL-4Rα epitope higher affinity than dupilumab**	**Patients with AD ≥12 years** **IGA: 3 or 4** **BSA: 10%+** **EASI: 16+** **NNRS**	RADIANT-AD Randomized 1:1 • rademikibart SC LD, then Q2W vs placebo 16 weeks then OLE x 36-week • rademikibart Q2W	259 patients 204 adults, 55 adolescents **Week 16:** **IGA 0/1 and ≥2-pt IGA reduction:** 47.7% vs. placebo 17.6% P < 0.0001 **EASI-75:** 74.2% vs. placebo 34.4% P < 0.0001 **EASI-90:** 43.0% vs. 14.5% P < 0.0001 ≥3-pt **Pruritus NRS reduction:** 54.7% vs. 27.5% P < 0.0001 **Week 52:** **IGA 0/1 and ≥2-point reduction:** 87.1% , **EASI-75:** 96.6% **EASI-90:** 85.3% , ≥3-pt Pruritus NRS reduction: 91.2% .	**Week 16** (R vs placebo) **SAE:** 2.3% vs 9% **DC:** 0.8% vs 0% **Week 52:** **SAE:** 5.5% **DC:** 0.8%

Intervention	Population	Protocol	Results	Adverse Effects
Roflumilast **Topical PDE4 inhibitor**	**Infants 3–24 months** **vIGA: 2–3** **BSA: 3%+**	INTEGUMENT-INFANT Phase 2 Open label study Roflumilast 0.05% cream once daily x 4 weeks	101 patients **Week 4:** **vIGA 0/1:** 49% **EASI-75:** 58.3% **WSI-NRS:** 60.6%	**Diarrhea:** 12.9% **Nasopharyngitis:** 8.9% **URTI:** 5.9%
Nemolizumab (anti-IL-31R Antibody)	**Children 2–11 years moderate–severe AD (EASI 16+)**	Open label Nemolizumab SC Q4W with topicals 52 weeks	**Week 16:** **EASI-75:** 64–73% **IGA success:** 40.5-47.2% Pruritis response up to 72% (sustained to Week 52)	**Asthma:** 2.7% **Conjunctivitis:** 3.7% **Bronchitis:** 10%
Dersimelagon (oral MC1R agonist)	**≥12 years** **Erythropoietic Porphyria /X-Linked Porphyria**	Phase 3 RCT (INSPIRE) 200 mg or 100 mg vs placebo 16 weeks	Improved sunlight tolerance (TTP +23 min) **Patient Global Impression of Change:** -1.83, P < 0.001 Reduction of total pain events: 39%, P = 0.004	Hyperpigmentation benign nevi headache GI (mostly mild)
Upadacitinib (oral JAK1 inhibitor)	**≥12 years** **non-segmental vitiligo (F-VASI ≥0.5, T-VASI ≥5)**	Phase 3 RCT (Viti-Up1+2) 15 mg daily vs placebo (2:1) 48 weeks	Viti-Up1 (n=205+101), Viti-Up2 (n=205+101) (phase 3 trials of upadacitinib) T-VASI50 ~19–21% vs 5.9% F-VASI75 ~23–25% vs ~6%	**URTI:** 10-14% vs 8-11% **Acne:** 11% vs 3-5% **NP:** 10-17% vs 8-14% No MACE or VTE

Table 1. Select late-breaking treatments for inflammatory dermatoses in pediatric populations; *courtesy of Cathryn Sibbald, MD.*

Abbreviations: AD: atopic dermatitis; **BSA:** Body surface area; **DC:** discontinuation; **EASI:** eczema area and severity index; **GI:** gastrointestinal; **IGA:** Investigator Global Assessment; **IL:** interleukin; **JAK1:** Janus kinase 1 inhibitor; **LD:** loading dose; **MACE:** major adverse cardiac events; **MC1R:** melanocortin 1 receptor, **vIGA:** validated IGA; **NNRS:** Numeric/Numerical Rating Scale (for pruritis); **NP:** Nasopharyngitis; **OLE:** Open Label extension, **PDE:** phosphodiesterase; **PP-NRS:** Peak Pruritis Rating Scale; **Q2W:** every 2 weeks; **Q4W:** every 4 weeks; **Q12W:** every 12 weeks; **RCT:** randomized controlled trial; **SAE:** serious adverse event; **SC:** subcutaneous; **VASI:** vitiligo assessment severity Index (**T:** Total, **F:** Facial); **URTI:** Upper Respiratory Tract Infection; **VTE:** venous thromboembolism; **WSI-NRS:** Worst Scratch/Itch Numeric Rating Scale

	Age and Weight	Dosing
Adalimumab	12–17 years, ≥30 kg	80 mg Week 0, 40 mg week 1 then q2W
Secukinumab	12–17 years, ≥30 kg to <90 kg	150 mg Weeks 0, 1, 2, 3, 4 then q4W
	12–17 years ≥90 kg	300 mg Weeks 0, 1, 2, 3, 4 then q4W

Table 2. FDA approved biologics for adolescents with hidradenitis suppurativa; *courtesy of Cathryn Sibbald, MD.*

Abbreviations: FDA: U.S. Food and Drug Administration; **Q2W:** every 2 weeks; **Q4W:** every 4 weeks

Systemic treatment options for pediatric psoriasis continue to expand, with recent phase 3 studies for guselkumab, risankizumab, and icotrokinra. The U.S. Food and Drug Administration (FDA) has approved guselkumab for children aged 6 years and older with plaque psoriasis, as well as icotrokinra for adolescents aged 12 years and older. Icotrokinra is a targeted oral peptide that blocks the IL-23 receptor. One-year results from the ICONIC-LEAD study were highlighted in poster format.[8] Sixty-six participants aged 12–17 years with psoriasis (body surface area ≥10%, a Psoriasis Assessment Severity Index response of 12, and Investigator Global Assessment ≥3) were randomized to icotrokinra once daily (n=44) or placebo (n=22) for 16 weeks followed by an open label extension in which all participants received icotrokinra. By week 24, >80% of those receiving icotrokinra had clear/almost clear skin, and >90% of those maintained that response through week 52. Minimal adverse effects were reported for all participants until week 52, with the most common being infections (n=31, 44%) with no serious infections and no adverse effects leading to discontinuation. The requirement to take icotrokinra on an empty stomach may be more of a deterrent for adult patients compared to adolescents, who are likely to be excited about avoiding needles and bloodwork monitoring.

Hidradenitis Suppurativa

Multiple speakers highlighted the recent FDA approval of secukinumab for adolescents aged 12 years or older with hidradenitis suppurativa, bringing the total number of biologics approved for hidradenitis suppurativa in this population to two (**Table 2**). Dosing recommendations were based on a model-informed drug development approach, resulting in tiered dosing recommendations that differ from pediatric dosing in psoriasis.

Trisomy 21

At the pre-AAD meeting for the Society of Pediatric Dermatology, novel insights were presented from several years of research into the key role of interferon signalling in trisomy 21.[9] Building on this background, an interventional study for Janus kinase (JAK) inhibitors was conducted in patients with trisomy 21 and at least one immune-mediated cutaneous condition (alopecia areata, psoriasis, hidradenitis suppurativa, vitiligo, and AD).[10] More than 40 participants completed 16 weeks of systemic JAK inhibitor therapy. Across 27.7 patient-years of observation, a single adverse event of thromboembolism was reported, occurring in a participant who was concurrently taking oral contraceptives. Clearly, additional data will help to define which patients with trisomy 21 would benefit most from oral JAK inhibitor treatments and how this treatment should be positioned in management plans.

Polycystic Ovarian Syndrome

An update on the approach and treatment of adolescents with polycystic ovarian syndrome (PCOS) was also presented at the pre-AAD meeting. Predictably, there is interest in the benefits of GLP1 agonists for this population. An ongoing interventional study is evaluating semaglutide administered over 10 months for restoration of ovulation in adolescents and adults with PCOS.[11] The results of the first eight participants were presented, with a median weight loss of 16.5% and median free testosterone

decrease of 51.8%. Six participants experienced an increase in menses frequency, one reported no change, and one reported a decrease in menses.

Chronic Spontaneous Urticaria

Guidelines now position dupilumab and remibrutinib alongside omalizumab as first line advanced therapies for chronic spontaneous urticaria (CSU) after the failure of antihistamines at up to four times the approved dose.[9] Unfortunately, only omalizumab remains approved in Canada for CSU in pediatric populations. Safety results for dupilumab in children aged 2–11 years with CSU were presented in poster format and are also available online (NCT05526521).[12] In this study, dupilumab at doses used for AD for 24 weeks was well tolerated in the 15 participants, with a follow-up interval of 36 weeks. Only a single injection site reaction was reported. Ongoing studies including this population will be essential to support the availability of targeted treatments for children with CSU.

Spitzoid Tumours

Dr. Elena Hawlryluk provided an update on spitzoid tumours in children, emphasizing that melanomas arising in spitzoid-appearing lesions are uncommon in children. Among adolescents, melanoma was identified in 13.3% of cases (51 of 384 lesions), compared to adults (50% risk if aged >50 years).[13] High risk clinicopathologic features of spitzoid tumours in pediatric and adolescent melanomas include age at diagnosis >10 years, clinical tumour diameter >1 cm, ulceration, involvement of subcutaneous fat, a mitotic rate of 6 mm^2 or more, high-grade cytologic atypia, and the presence of an expansile dermal nodule.[9] She also reviewed recommended margins for excision spitzoid tumours.[9] In pediatric populations with atypical spitz tumours or non-spitzoid melanocytomas excised with positive margins, the recommendation is to re-excise with 1-3 mm margins without the need for sentinel node biopsy. If the tumour does not extend to the biopsy margins, no further excision is recommended. Sentinel lymph node biopsies are not recommended in either of these clinical scenarios.

Acne

During the hot topics session, Dr. Amy Flischel presented data from two recent studies with particular relevance to adolescent patients with acne. The first was an open label study evaluating an LED mask delivering combined 415-nm and 633-nm phototherapy (Omnilux Clear), which reported a mean decrease of inflammatory counts of 13.07 (standard deviation [SD] 7.29) and non-inflammatory counts of 14.73 (SD 10.86) after 7 weeks, with investigators noting improvements in erythema in 66% of patients.[14] Although interpretation is limited by the inherent biases of an open label study design, this data is helpful in providing some safety information for patients who are interested in these devices. Dr Flischel also reviewed findings from a large database study of over 20,000 patients, which reported a significantly increased risk of acne associated with hormonal intrauterine devices compared to copper devices, with incidence rates following insertion of 1.5% at 1 year, 2.8% at 3 years, and 3.6% at 5 years.[15]

Juvenile Dermatomyositis

Dr. Leslie Castelo-Soccio presented new insights into the pathogenesis and treatment of juvenile dermatomyositis (JDM). She reviewed recent data that reported on unique cytokine profiles according to antibody positivity.[16] In patients with anti–melanoma differentiation-associated protein 5 (MDA5) associated JDM, elevated levels of interferon-α (IFN-α), IL-18, and CXCL9 were observed and were associated with lung involvement. In contrast, anti–nuclear matrix protein 2 (NXP2) disease was characterized by elevated soluble tumour necrosis factor receptor II (sTNF-RII) and IL-6 levels, correlating with muscle injury. Patients with anti–transcriptional intermediary factor 1 gamma (TIF1γ) demonstrated only modest cytokine elevations, suggesting a distinct inflammatory profile.

Dr. Castelo-Soccio also highlighted the utility of examining capillary dropout in nails using dermoscopy as well as visual assessment of gingival capillaries with the naked eye to

monitor disease activity. Finally, she reviewed a growing amount of evidence supporting targeted treatments in JDM, including over 100 reports of successful systemic JAK inhibitor treatments (most commonly with ruxolitinib or baricitinib). Additional emerging data included treatment of refractory adolescents treated with anifrolimab, an interferon targeted therapy, and reports of children with refractory anti-TIF1γ disease treated with dazukibart, a monoclonal antibody targeting interferon beta.

Vitiligo

Speakers in the vitiligo sessions presented data demonstrating improvement in repigmentation outcomes with the addition of phototherapy to multiple emerging targeted therapies, including topical ruxolitinib and systemic ritlecitinib.[17,18] Practical tips on the use of topical ruxolitinib in clinical practice were discussed. While participants in clinical trials were asked to wait up to 2 hours before applying makeup or creams, in real-world settings, 30 minutes was recommended to allow for optimized morning applications. Resources to support patients and providers using home phototherapy, including treatment instructions and tracking logs, are available through the Global Vitiligo Foundation (**globalvitiligofoundation.org**).

Numerous other high-yield and engaging sessions, along with valuable opportunities to meet and connect with colleagues, contributed to an overall excellent meeting experience. Next year's meeting will be in San Francisco from March 19-23, 2027.

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C.S.: None declared.

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Seeing More Than Meets the Eye: Artificial Intelligence-Based Imaging in Dermatology and the Future of Equitable Care

Sheila Wang, MD, PhD, FRCPC

Introduction

Artificial intelligence (AI)-based imaging is rapidly reshaping how skin disease is documented, triaged, and monitored, yet its clinical adoption still lags far behind its technological promise.[1-10] This gap is especially pressing for patients with skin of colour (SOC) and others who already experience barriers to dermatologic care.

What AI Actually Does in Dermatology

AI refers to computer programs designed to perform tasks that simulate human intelligence, including learning from data, recognizing patterns, and making decisions. Within health care, AI systems are increasingly used to support clinicians by enabling more consistent interpretation of complex information at scale and is intended to augment, rather than replace, clinical judgment.[1,2]



Figure 1. Smartphone-based AI wound imaging at the point of care; A clinician uses a smartphone application to capture a standardized wound image with automated boundary detection and area calculation, illustrating how AI-enabled imaging can support objective measurement and longitudinal monitoring in everyday clinical settings, including primary care and community practice; Smartphone-based wound imaging was performed using the Swift Ray 1 platform; *courtesy of Swift Medical Inc., Toronto, Canada.*

In dermatology, most current tools fall under visual AI, or computer vision, which focuses on interpreting images and videos to support clinical tasks. Common imaging tasks include classification (assigning a diagnosis), detection (localizing a lesion), and segmentation (outlining a lesion), each supporting different aspects of care such as triage, biopsy decision-making, and longitudinal follow-up. Deep learning approaches, particularly convolutional neural networks, can learn subtle image features directly from pixel data and have demonstrated dermatologist-level performance for certain skin cancer classification tasks in research settings.[3,11]

Because skin disease can manifest across multiple visual scales, AI methods have been applied to clinical photography, dermoscopy, dermatopathology, and teledermatology imaging. In practice, many systems are deployed as clinical decision-support tools that suggest likely diagnoses, highlight regions of interest, or provide standardized measurements over time rather than offering stand-alone diagnostic decisions (**Figure 1**). More recently, vision-language and other multimodal architectures have been proposed that integrate both image and textual information, creating opportunities for richer, context-aware decision support.[3,12]

Despite rapid growth in the research literature, regulatory approval of dermatology AI tools remains limited. A recent review identified only a small number of AI-based dermatology

devices with regulatory clearance worldwide, including just a few systems authorized by the United States Food and Drug Administration, in sharp contrast to the hundreds of AI-enabled devices in radiology. Lengthy medical device approval timelines and the relative novelty of adaptive algorithms within existing regulatory frameworks contribute to this slower uptake.

Why Performance in Practice Often Falls Short

Many AI systems demonstrate impressive accuracy in curated research datasets but perform less reliably in day-to-day practice. This performance gap reflects how dermatologic data are collected, labelled, and evaluated.[8,10,13-15]

Most training datasets comprise images captured under relatively controlled lighting and camera conditions and are often drawn from specialist centres rather than primary care clinics or patient homes. In these settings, models may inadvertently learn spurious correlations, such as device-specific artifacts, background patterns, or image quality, rather than lesion morphology itself, leading to brittle performance when deployed across different environments.

Establishing robust ground truth represents another challenge. Many datasets rely on single-clinician assessments without histopathologic confirmation or longitudinal follow-up, and details of labelling workflows are often underreported.[5,8,10,13-15] Well-documented inter-rater variability in diagnosis and severity scoring, especially for inflammatory skin diseases, further undermines label reliability and limits its generalizability. Together, these issues contribute to discrepancies between algorithm performance reported in development studies and effectiveness in routine care.

External validation is frequently limited, and relatively few studies evaluate AI performance prospectively in real-world workflows. A systematic review comparing AI systems with clinicians for skin cancer diagnosis found that most studies relied on retrospective data rather than prospective trials. In studies that have included randomized or prospective designs, AI assistance tends to function best as an adjunct to clinician judgment, helping to improve diagnostic accuracy particularly for generalist physicians, rather than as an independent diagnostic system.[2]

The Blind Spot: Skin of Colour and Dataset Bias

Underrepresentation of SOC is one of the most critical limitations of current dermatologic AI systems. Many training datasets disproportionately contain images of lighter skin tones and classic "textbook" disease presentations, whereas darker skin, early or subtle disease, and treatment-modified lesions are often underrepresented. These imbalances mirror long-standing inequities in dermatology education, research, and workforce representation and risk perpetuating the same disparities within AI tools.[5,7,16,17]

Dermatology also lacks a robust, standardized approach to measuring skin tone for AI development and evaluation. Much of the literature has used the Fitzpatrick skin type, a classification system designed to capture sun reactivity rather than actual skin pigmentation and performs poorly in those with SOC.[16,17] This limitation can distort both malignancy risk assessment and evaluations of model performance across skin tones. Without careful skin tone characterization and stratified reporting, apparent "overall" accuracy can mask substantially worse performance in darker skin.[5,7,16,17]

Alternative frameworks, such as the Monk Skin Tone Scale, were specifically developed to better represent a continuum of pigmentation across diverse populations and may offer a more appropriate foundation for skin tone-stratified evaluation in dermatologic AI.[18] Regardless of the specific scale, intentional sampling strategies, transparent reporting of skin tone distribution, and skin tone-stratified performance metrics should be adopted as standard practice.

Evidence from curated image datasets and systematic reviews demonstrates that AI models may show lower sensitivity for melanoma in patients with SOC compared with pooled performance across all skin types, raising concern that uncritical deployment could inadvertently exacerbate existing outcome gaps. At the

same time, much of the oncology-focused AI literature has been generated in predominantly lighter-skinned populations, highlighting a clear need for more inclusive data and evaluation.[5,7,16,17]

Beyond the Image: Multimodal and Context-Aware Models

Most dermatology AI tools are image-only models that do not incorporate clinical history, risk factors, or treatment context. In everyday practice, morphology is only one part of the diagnostic puzzle, particularly for inflammatory dermatoses, drug eruptions, pigmentary disorders, and complex presentations where pattern recognition alone is insufficient.[4,5,19]

Multimodal approaches that combine imaging with structured metadata, such as age, sex, cancer history, or lesion evolution, have already demonstrated superior performance to image-only models for common malignant and benign lesions.[5] For example, models that combine smartphone photographs with patient metadata have improved overall diagnostic accuracy and discrimination for distinguishing between malignancies and benign lesions in clinically relevant classes (**Figure 2**). Vision-language systems and transformer-based architectures are also emerging, offering the potential to jointly process clinical notes, patient-reported symptoms, and images in a single pipeline.[3]

From a clinician's perspective, AI is most often valuable not as a source of definitive diagnoses but as a tool for risk stratification, helping determine which lesions can be monitored, which warrant biopsy, and which require urgent referral.[4-7,11,13] In this context, calibrated risk outputs, clear uncertainty estimates, and intuitive visual explanations may be more useful than rigid categorical labels.

Health Equity: Risks and Opportunities

The same technologies that risk amplifying disparities can, if deliberately designed, help reduce them.[4,5,8,16,17,18,20] AI-augmented teledermatology has expanded access to specialist expertise through both real-time video and asynchronous "store-and-forward" models. For



Figure 2. Thermal and segmentation-based assessment of cutaneous inflammation; Example screenshots from an AI-enabled mobile platform showing thermal maps and automated lesion segmentation, demonstrating how multimodal imaging can highlight areas of subclinical inflammation and provide consistent, quantitative metrics for disease activity over time, particularly useful for poorly demarcated inflammatory dermatoses in people with skin of colour; *courtesy of Swift Medical Inc., Toronto, Canada.*

patients in remote, rural, or otherwise underserved settings, AI-enabled mobile applications can provide preliminary lesion assessment, triage recommendations, or monitoring support that might otherwise be unavailable.

Patients from marginalized groups may view algorithmic decision-making as one potential way to reduce exposure to implicit bias encountered in traditional care, although this depends heavily on the transparency and validation of the tools. Equity-centred design therefore requires diverse training data, rigorous bias assessment, transparent reporting, and meaningful

engagement with the communities most likely to be affected.[5,15-17]

Large language models (LLMs) can also help address communication barriers in dermatologic care. Early evidence suggests that LLMs can simplify patient-education materials, improve readability, and generate multilingual content tailored to different literacy levels, which may be particularly valuable for newcomers and patients with limited health literacy.[4,5,8,16,17,20] Wearable and sensor-based technologies, including devices that monitor scratching or skin temperature, offer additional opportunities for low-cost, remote monitoring of chronic skin disease, particularly in settings with limited specialist access.

Building Trustworthy, Clinically Useful AI

Moving from proof-of-concept models to trustworthy, widely adopted tools in dermatology will require sustained attention to data quality, transparency, and evaluation.[4,5,8,10,13-15]

Several priorities stand out:

- Representative training and validation datasets that intentionally include diverse skin tones, care settings, body sites, ages, and disease severities, with explicit reporting of these characteristics.
- Robust ground truth anchored in histopathology or well-documented clinical follow-up wherever feasible, with clear reporting of labelling methods and inter-rater agreement when consensus labels are used.[4,5,8,10,13-15]
- Prospective, real-world studies embedded in clinical workflows to evaluate impact on diagnostic accuracy, biopsy rates, wait times, and patient outcomes.[2]
- Routine skin tone-stratified reporting of sensitivity, specificity, and calibration, accompanied by transparent discussion of any performance gaps and efforts to address them.
- Human-AI collaboration models designed to augment clinician judgment, supported by intuitive interfaces, clear communication of uncertainty, and integration into existing electronic medical record systems.
- Post-deployment monitoring frameworks to track safety, performance drift, and equity across patient groups over time.[5,8-10,14,15]

Dermatology is a highly visual, pattern-based specialty in which AI holds intuitive appeal. Yet the conditions most in need of improved access and equity, including chronic inflammatory diseases, pigmentary disorders, and malignancies in patients with SOC, are also those least likely to be well represented in existing training datasets. Thoughtfully designed, clinically integrated, and equity-focused AI has the potential to move the field beyond isolated lesion classification toward comprehensive, longitudinal, and patient-centred skin health, allowing us to see, and act on, more than meets the eye.[4-6,8,10,11,13,16-18,20]

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Safety and Monitoring Update on Isotretinoin

Vincent Richer, MD, FRCPC

Introduction

Canadian dermatologists frequently encounter fear and misconceptions of isotretinoin among patients and the general public. In contrast, few medications in dermatology have been as transformative: since its introduction, isotretinoin has dramatically changed the treatment of acne through its potential for providing long-term remission (**Figure 1**). Initial consultations in which isotretinoin is proposed are often lengthy and emotionally charged, with substantial discussion devoted to drug safety, treatment monitoring, and risk-mitigation strategies. This article provides an evidence-based update on select safety concerns surrounding isotretinoin, including well-established and serious risks, concerns that have been confidently refuted, and some less common issues frequently raised by patients based on their own research.

Pregnancy and Teratogenicity

Unlike some of the more controversial concerns surrounding isotretinoin, its teratogenic effects are unequivocal and remain the single most critical safety consideration when prescribing this medication to women of childbearing potential.

In Canada, 3.1 pregnancies per 1,000 female isotretinoin users were reported between 1996 and 2011.[1] In the United States, isotretinoin use is tightly regulated via iPLEDGE, a mandatory United States-Food and Drug Administration safety program designed to prevent fetal exposure to isotretinoin. Despite this, 3,347 isotretinoin-exposed pregnancies were reported in the United States from 2006–2020.[2]

With this in mind, prescribing isotretinoin requires disclosure of this risk, discussion about sexual activity and the potential for pregnancy, establishment of appropriate contraception, routine urine pregnancy testing, and clear

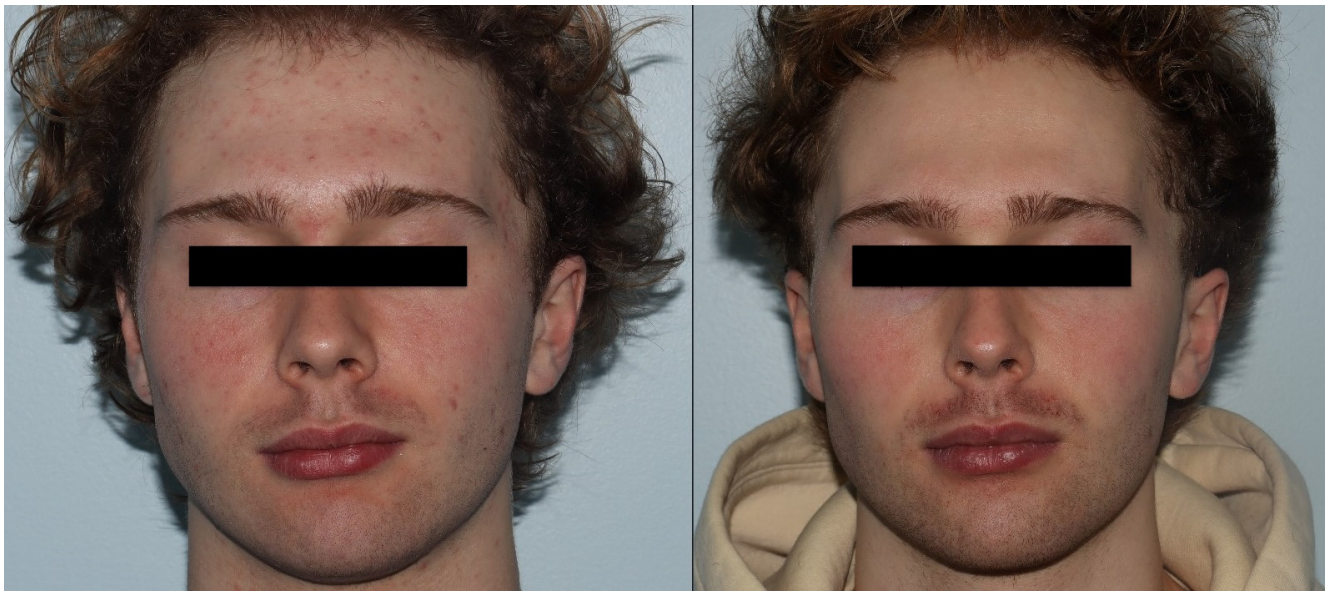


Figure 1. Moderate persistent acne that was insufficiently responsive to topical treatments in an adult patient treated with isotretinoin. The potential for long-term remission with isotretinoin treatment coupled with an improved understanding of its safety profile has allowed for an expansion of its clinical indications in the Canadian practice landscape; *courtesy of Vincent Richer, MD, FRCPC*.

counselling about the indication for a medical abortion in the event of a pregnancy during treatment. A key challenge is achieving an appropriate balance between the safe use of the treatment and maintaining access without imposing unnecessary regulatory burdens.

Depression and Mental Health

A possible link between isotretinoin and depression remains one of the most emotionally charged issues in dermatology. Historically, case reports and anecdotal experiences raised concerns that isotretinoin might directly trigger depression, anxiety, or suicidal ideation. These concerns led to the introduction of black box warnings and the recommendation for extensive psychiatric screening protocols.

The challenge in interpreting this link is that patients with severe acne causing scars were being treated with isotretinoin, a condition that is itself strongly associated with depression, social withdrawal, anxiety, and reduced quality of life.[3] Treatment of acne with multiple modalities has been demonstrated to improve quality of life and reduce depression scores. Large retrospective cohort studies and meta-analyses have failed to demonstrate a causal relationship between isotretinoin and depression in the general population. In fact, many reports suggest a positive impact on quality of life and mental health in patients who complete treatment with isotretinoin.[4] However, these findings are counter-balanced by adverse event reporting databases that continue to collect individual cases of mood disorders, including suicidal ideation, during treatment.

This nuance is best addressed directly in discussions with patients. Current evidence does not suggest that isotretinoin universally increases depression risk, however, some individuals may experience idiosyncratic mood changes during treatment. Notably, acne itself is a major confounding factor. Rather, many dermatologists have observed improvements in psychological well-being and self-confidence among their patients during treatment.

Inflammatory Bowel Disease

The possible association between isotretinoin and inflammatory bowel disease (IBD) has been debated for years; however, this controversy is one that has been more clearly refuted. Early

observational studies and class action lawsuits amplified public concern, leading many patients to believe that isotretinoin directly causes IBD.

The association between IBD and isotretinoin does not persist when controlling for factors such as antibiotic use, acne severity, and oral contraceptive use.[4] It is unclear if prolonged antibiotic use in the context of acne treatment may induce gut microbiome dysbiosis and affect IBD development risk. Furthermore, severe acne and inflammatory disorders may share underlying immune or genetic predispositions independent of isotretinoin exposure. These variables have been confirmed as confounders in large cohort analyses. For example, the TriNetX network study compared more than 81,000 exposed patients with 1.9 million controls and reported very reassuring hazard ratios (HR): IBD overall (HR: 0.88, 95% confidence interval [CI]: 0.49–1.57), ulcerative colitis5 (HR: 1.05, 95% CI: 0.78–1.41), and Crohn's disease (HR: 0.69, 95% CI: 0.51–0.94).

In light of such reassuring datasets, most experts do not consider isotretinoin a proven cause of IBD.

Peanut Allergy and Isotretinoin

Canadian dermatologists may be surprised to note that peanut allergy is mentioned as a contra-indication to treatment with isotretinoin in the British and European product monographs. However, isotretinoin formulations contain no peanut protein; this labelling stems from historical concerns of cross-reactivity between peanuts and soy, as both are legumes. Isotretinoin is often formulated in refined soybean oil, which is considered safe not only for patients with peanut allergy but is also considered generally safe for patients with soy allergy. Patients with clinical and prick-test positive peanut allergy have been successfully and safely treated with isotretinoin.[6]

Premature Closure of Epiphyseal Plates

Premature epiphyseal plate closure is a rare but important theoretical concern associated with systemic retinoids, and is likely to be a concern for the parents of children who have not yet reached full growth, especially if their anticipated height may be below average.

Although isolated case reports exist in the literature, usually in the context of high-dose treatment in oncology, clinically significant growth disturbances from standard acne dosing remain exceptionally uncommon. A recent publication analyzed insurance data from 2005–2021 and used patients treated with antibiotics as the control group.[7] While a reduced height velocity was observed during treatment with isotretinoin, there was no difference in the final adult height between the groups.

Overall, current evidence does not support widespread concern regarding growth impairment with typical isotretinoin treatment courses used for acne in preadolescents—a population in whom severe acne may have the greatest long-term psychosocial and scarring consequences.

Diminished Night Vision

One of the other considerations during isotretinoin treatment is diminished night vision. Though this effect is rarely reported by patients, it is thought to be potentially problematic for pilot performance.[8] The Federal Aviation Agency recommends restricting the use of isotretinoin to >2 weeks before flying; otherwise a medical exam or clearance is required to fly. This constitutes another factor to consider when weighing the risks and benefits of treatment, particularly for student pilots.

Laboratory Monitoring

While routine monthly pregnancy tests continue to be recommended during isotretinoin treatment, laboratory monitoring of liver enzymes, lipids, and other parameters has come under significant scrutiny in recent years. The intensive monitoring schedule highlighted in the original Accutane© monograph (every 1–2 weeks initially!) had already been challenged in clinical practice prior to systematic reviews, meta-analyses, and letters to the editor began calling for reduced laboratory monitoring more than a decade ago.[9]

Laboratory changes from baseline were overwhelmingly not clinically relevant, and

usually emerge within 8 weeks of the initiation of treatment.[10] In the absence of liver disease or metabolic syndrome, it has been recommended to assess liver enzymes and lipids at baseline and again at 8 weeks, with further follow-up on any identified abnormalities only. Routine complete blood count (CBC) monitoring is no longer recommended in the absence of preexisting abnormalities.

Recent articles extend this discussion further in the pediatric population, suggesting that decisions regarding laboratory monitoring should be customized to the individual given the rarity of severe side effects and the lack of evidence of preventable adverse outcomes. In a pediatric outpatient clinic study, 165 patients underwent 708 laboratory tests; all laboratory abnormalities were attributed to preexisting baseline findings or non-fasting samples.[11]

Furthermore, new evidence highlights that laboratory monitoring practices may reflect gender bias. Female patients are more likely to undergo more CBC, liver function, and lipid laboratory testing, likely due to these tests being ordered simultaneously with pregnancy testing as part of standing orders, rather than requested based on clinical indications.[12] Authors also emphasize that urine pregnancy tests are preferred over serum testing, both to reduce health care costs and to avoid the risk of false-positive results in the context of anti-heterophile antibodies.

Isotretinoin in the Era of Modern Medicine: Telemedicine and Artificial Intelligence

Although the application and practicality of telemedicine in dermatology has been limited in scope, acne is one of the conditions that can be treated reliably via remote care. A recent study[13] examined the rate of incomplete isotretinoin courses delivered via telemedicine and compared them to with those from in-person adult and pediatric clinics. While 27% of telemedicine-treated courses were incomplete, higher rates were observed in in-person adult (37%) and in-person pediatric (49%) clinics. These findings suggest that telemedicine is well-suited to providing ongoing access to isotretinoin.

Lastly, patients are increasingly turning to artificial intelligence (AI) chatbots for medical information. When evaluated systematically and compared, commonly used AI chatbots provided accurate information, with ChatGPT and Gemini outperforming Copilot.[14] However, all systems scored comparatively poorly on readability, highlighting the need for future AI models to better account for the limited health literacy of the general public.

Conclusion

One of the challenges with prescribing isotretinoin is that it exists at the intersection of dermatology, medicine, psychology, internet culture, and historical controversy. Patients often arrive having encountered alarming information online—some of which is legitimate, while other concerns are disproportionately amplified beyond what the evidence supports. The clinician's responsibility is not to oversimplify in either direction, but to engage in a balanced and nuanced discussion of risks and benefits with our patients. Isotretinoin remains one of our most valuable tools—not because it is risk-free, but because its long-term benefits are well established and its risks are well defined and manageable.

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