Advances in the Etiology, Detection, and Clinical Management of Seborrheic Keratoses

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Keywords
Seborrheic keratosis · Oncogenic mutations · Dermoscopy · Artificial intelligence · Noninvasive diagnostics · Topical therapies

Abstract
Seborrheic keratoses (SKs) are ubiquitous, generally benign skin tumors that exhibit high clinical variability. While age is a known risk factor, the precise roles of UV exposure and immune abnormalities are currently unclear. The underlying mechanisms of this benign disorder are paradoxically driven by oncogenic mutations and may have profound implications for our understanding of the malignant state. Advances in molecular pathogenesis suggest that inhibition of Akt and APP, as well as existing treatments for skin cancer, may have therapeutic potential in SK. Dermoscopic criteria have also become increasingly important to the accurate detection of SK, and other noninvasive diagnostic methods, such as reflectance confocal microscopy and optical coherence tomography, are rapidly developing. Given their ability to mimic malignant tumors, SK cases are often used to train artificial intelligence-based algorithms in the computerized detection of skin disease. These technologies are becoming increasingly accurate and have the potential to significantly augment clinical practice. Current treatment options for SK cause discomfort and can lead to adverse post-treatment effects, especially in skin of color. In light of the discontinuation of ESKATA in late 2019, promising alternatives, such as nitric-zinc and trichloroacetic acid topicals, should be further developed. There is also a need for larger, head-to-head trials of emerging laser therapies to ensure that future treatment standards address diverse patient needs.

Introduction
Seborrheic keratoses (SKs) are the most common epithelial tumor encountered in clinical practice and diagnosed in teleconsultations [1–4]. These lesions are primarily benign, highly biopsied, and typically removed for cosmetic reasons, though eruptive presentations like the Leser-Trélat sign can indicate malignancy [5–8]. A national data profile of skin disease estimates that SK affects nearly 84 million Americans and incurs over USD 1.2B in annual medical costs [9]. Notably, 85% of all SK patients who seek medical treatment present to dermatologists [6]. SKs are, therefore, recognized as a frequent cause of dermatologic visits that create important opportunities
for detecting other skin disorders [10]. Despite their high prevalence and large cost burden, SKs are not widely discussed in the current literature. Furthermore, treatment options are often uncomfortable and have cosmetic sequelae. In this review, we highlight advances in SK pathogenesis, discuss novel noninvasive diagnostics, and provide an overview of emerging topical and laser therapies.

Clinical Presentation

SKs develop in hair-bearing areas and most commonly occur on the head, neck, trunk, and extremities, while sparing mucous membranes and the palms and soles [10, 11]. Rare cases of lesions in the external ear [12–14] and pedunculated tumors in perigenital areas have been reported [15–17], as well as truncal lesions along Blaschko’s lines [18, 19]. SKs are generally asymptomatic and present as papules, macules, and plaques. Most variants range in color from tan to black and are well-demarcated with a verrucous, “stuck-on” appearance. Surface textures can be waxy, keratotic, scaly, or greasy appearing and may become rougher over time [10, 20]. SKs may also undergo exophytic, hyperplastic, and/or hyperpigmented change [21]. Lesions continue to develop over the lifespan and can grow to >5 cm in diameter [11]. Spontaneous regression is rare.

Patients presenting with SK are often concerned about the possibility of skin cancer and their aesthetic appearance, as an estimated one-third of SK patients present with greater than 15 lesions [10]. An observational study of 406 adult patients found that asymptomatic SK removals were due to nonmutually exclusive concerns about more serious illness (57%), cosmetic reasons (53%), tactile discomfort (44%), and irritation or itchiness (42%), with most patients having taken measures to "disguise, hide, or deal with" their SKs [22]. Individuals with multiple lesions on the face, hands, genitals, and other sensitive areas may suffer from perceived disfigurement and experience negative psychological impacts [23]. Furthermore, lesions may become inflamed (irritated SK) due to trauma or secondary infection and cause pain, pruritus, erythema, or crusting.

Epidemiology

SKs are highly prevalent in older populations and seem to increase with age. In a recent retrospective cohort study of 10,545 Brazilian patients older than 60 years, this disorder was the leading cause for dermatologic teleconsultations. Eighty-nine percent of lesions occurred in patients aged 80 years and above [2]. Previous studies of dermatology patients in Australia, the United Kingdom, the Netherlands, and Korea found similarly high, strongly age-related prevalence, as well as higher average numbers and diameters of SK lesions in geriatric individuals [24–27]. However, SKs can also develop at younger ages. Another Australian study of 170 people aged 15–30 years found that 24% had at least 1 lesion, 78% of which were truncal [24, 28]. Though pediatric dermatologists do not typically encounter SKs, the dermatosis papulosa nigra (DPN) variant has specifically been observed in children [10, 29–31].

SKs are mainly noted as coincidental findings in epidemiologic research, and relatively little is known about their demographic distribution. Recent studies have not found significant gender differences in SK incidence, though an observational study found that men exhibited more lesions on the trunk and arms than women [2, 11, 22, 24, 32]. While a Caucasian predominance has been assumed, SKs occur with near-equivalent incidence in Korean males (Fitzpatrick I–V) as in Caucasians and are generally known to occur in diverse skin types [26]. DPN is found more often in African American, East Asian, and South Asian populations (Fitzpatrick IV–VI) with a consistently reported predominance in women and is thought to be underrecognized [33–36]. There is a high likelihood of family history, especially in individuals with large numbers of lesions [37–41]. Autosomal dominant inheritance with incomplete penetrance has been proposed [11, 40, 42].

Etiology and Molecular Pathogenesis

Risk Factors

UV exposure has been implicated in the etiopathology of SK, though causality remains unclear. An Australian study found more frequent, flatter, and larger lesions in sun-exposed body sites, as well as higher SK prevalence when compared to other Caucasian populations in the United Kingdom [24]. Similarly, the aforementioned study of Korean males found lesions concentrated on the face and backs of the hands, as well as a 2.28-fold higher risk of SK associated with lifetime sunlight exposures of over 6 h/day versus less than 3 h/day [26]. A survey of 840 people in China also found a relationship between cumulative UV exposure and SK, noting that residents with Fitzpatrick II skin types were susceptible to more severe
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Lesional skin can be attributed to markedly upregulated secretion of EDN-1 production-inducing cytokine TNF-α [63, 64]. EDN-1 is a keratinocyte-derived mitogen and strong melanogen in human skin cells [64]. Additionally, a recent study of 400 Chinese women found an association between SK incidence and smoking [65]. Meta-analyses have linked smoking to atopic dermatitis, psoriasis, and lupus erythematosus risk [66–68].

Oncogenic Activation

Despite their benign nature, a large proportion of SKs exhibit oncogenic mutations. A somatic mutation in fibroblast growth factor receptor 3 (FGFR3), identical to those associated with skeletal dysplasia and urogenital neoplasms, is correlated with age and body site in SK patients [42, 69–71]. Though activated FGFR3 and its receptors demonstrate oncogenic function in solid tumors [72–74], oncogene-induced senescence is not observed in SK [75]. Furthermore, the mild epidermal hyperplasia caused by FGFR3 mutations cannot independently drive tumorigenesis [76]. This may be explained by a positive FGFR3/FOXL1 feedback loop in SK, where increased FGFR3 activity induces FOXL1-led differentiation and triggers a benign SK-like phenotype in previously malignant squamous cell carcinoma (SCC) cells. Conversely, FOXL1 knockdown augments oncogenic RAS and results in SCC-like tumors [77, 78]. Fibroblast growth factor deficiency also causes epidermal defects associated with inflammatory dermatoses, and epidermal growth factor receptor (EGFR) has been implicated in abnormal keratinocyte proliferation and differentiation in SK [79–81].

In recent years, additional oncogenic mutations have been elucidated. A mutation in the p110α catalytic subunit of phosphatidylinositol 3-kinase (PIK3CA), which co-occurs with FGFR3 mutations in malignant bladder tumors, also co-occurs with PIK3CA mutations in SK [12, 40, 78, 82, 83]. A mutational screen of 175 SKs for FGFR3-RAS-MAPK and PI3K-AKT pathways found additional mutations in KRAS, HRAS, EGFR, and AKT1 oncogenes. However, tumor suppressors TSC1 and PTEN were not mutated and, as previously illustrated in FGFR3 studies, senescence and DNA damage responses were absent despite oncogenic activation. Unlike similarly mutated neoplasms, SKs are genetically stable [84].

SKs show increased rates of proliferation and apoptotic suppression when compared to normal keratinocytes [42, 85]. Akt kinase signaling, which interacts with FGFR3 and p110α proteins, inhibits the p53 pathway and FOXO-mediated apoptosis in SK. In contrast to cutaneous SCC, SK does not show mutations of p53, which suggests that this gene plays a differential role in sensitivity to UV-induced keratinocyte senescence, where the production of uric acid generates reactive oxygen species and damages DNA [47]. Intriguingly, GDA also appears to promote melanogenesis by upregulating stem cell factor (SCF) and endothelin (EDN)-1 in epidermal keratinocytes and may, therefore, play a role in many hyperpigmentary skin disorders [48].

Viral etiologies have also been suggested, as human papillomavirus (HPV) DNA has been found in up to half of SK specimens across various studies [49–56]. However, rates of HPV detection tend to be much higher in genital versus nongenital SKs. A 2004 study found that SK had 79% HPV positivity on lesion surfaces versus 19% in biopsies, suggesting that positivity may simply reflect surface contamination [57]. Additionally, more recent studies could not replicate high levels of HPV detection in SKs [58–60]. Merkel cell polyomavirus was recently detected in 26% of reviewed SKs, but was ascribed to coincidental coinfection; these viruses replicate in rapidly dividing cells [51, 61].

Immune factors are newly implicated in SK. Mast cells are significantly increased at the periphery of SK tumors, and mast cells, SCF, and cannabinoid receptor type 1 (CB1) are differentially expressed within them [62]. This novel mechanism suggests that immune components involved in inflammatory dermatoses may also play a role in SK pathogenesis. Another study found that while the paracrine cytokine SCF and its receptor c-KIT are surprisingly downregulated in SK, high levels of EDN-1 in lesional skin can be attributed to markedly upregulated FOXN1 activity induces FGFR3-mediated differentiation and FGFR3 feedback loop in SK, where increased FGFR3 expression also causes epidermal defects associated with inflammatory dermatoses, and epidermal growth factor receptor (EGFR) has been implicated in abnormal keratinocyte proliferation and differentiation in SK [79–81].

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to Akt inhibition. Differential expression of tumor suppressors p16 and p27 is found in various SK subsets, especially clonal SK, and p53 and p16 overexpression in irritated SK may also indicate a pathway for malignant tumor transformation or adjacency (“collision tumors”) [61, 86–92]. Furthermore, elevated phosphorylated Akt in SK may confer hypersensitivity to apoptotic inhibition [89]. Paradoxical findings of “oncogenic driver” mutations in this benign disorder have profound implications for tumorigenesis research and the future treatment of skin tumors [93, 94].

These and other emerging theories of SK pathogenesis are speculatively summarized in Figure 1.

**Noninvasive Diagnostics**

SK lesions that resemble melanocytic neoplasms can be challenging to diagnose with the naked eye [5, 95, 96]. A clinicopathologic review of skin biopsies in 8,694 patients found that 30% of excised SKs were misdiagnosed as nonmelanocytic skin cancer and 3% as melanoma.

Fig. 1. Proposed mechanisms of pathogenesis mediated by aging, UV exposure, and immune-related factors.
Twenty-one percent of all misdiagnosed cutaneous melanoma cases were determined to be SKs or benign nevi [97]. An assessment of 367 basal cell carcinoma (BCC) cases similarly found that 22% of misdiagnosed cases were SKs [98]. Malignancy tends to be overdiagnosed, reflecting a cautious approach to the management of skin tumors and an opportunity for advanced imaging techniques to augment clinical detection. Furthermore, data from SKs plays an important role in the development of artificial intelligence (AI)-based skin lesion detection technologies.

**Dermoscopy**

Dermoscopy is a powerful technique for visualizing clinically inapparent diagnostic features in real time. Though other methods have superior resolution, dermoscopy is the most widely used due to its ease of use and availability [99]. Notably, polarized and nonpolarized dermoscopy differ in their ability to visualize different features and should be used complementarily [100]. The two-step algorithm for dermoscopic SK diagnosis organizes features into (1) exclusionary criteria of a pigment network, aggregated globules, and homogenous patterns of blue pigmentation and (2) inclusionary criteria of fissures and ridges, comedo-like openings, milia-like cysts, and brown fingerprint-like structures as shown in Figure 2 [101]. Subsequent studies report additional features, including hairpin vessels, sharp demarcation, moth-eaten borders, crypts, and exophytic papillary structures [102, 103]. A prospective study of 416 lesions found that the inclusion of a lack of blue-grey/white color, presence of yellowish color, and mica-like structure further optimizes SK identification [104].

In general, the above features constitute important findings for SK [20, 96, 100, 102, 105–107]. They are used in dermoscopic scoring methods shown to improve clinical accuracy for distinguishing between SKs and SK-like melanomas [108, 109]. A subgroup of these features, including hairpin vessels, a diffuse regular vessel arrangement, and 10% lesion coverage with white halos, can be used to differentiate irritated SK and SCC [110]. However, a global pattern has not been identified for atypical SKs. A study of 72 biopsies found that some of these lesions actually exhibit non-SK features, including a blue-whitish veil, polymorphous vessels, globules, and white streaks [111].

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**Fig. 2.** Illustrated summary of key dermoscopic inclusion criteria for seborrheic keratosis (right), with accompanying dermoscopic images of milia-like cysts and fissures and ridges features (left). Images are adapted from Dermoscopedia.org under the Creative Commons Attribution 4.0 International License.
Several dermoscopy-dependent imaging techniques have been developed, including videodermoscopy (sequential digital dermoscopy) and computer-assisted digital dermoscopy. The latter involves an integrated approach for the objective measurement of multiple parameters in an assisted diagnosis model that are then analyzed as possible discriminant variables. This integration of numerical features, dermoscopic patterns, and personal metadata was initially performed in melanoma but could be replicated for SK [112]. In conjunction with dermoscopic data, information from multispectral digital skin lesion analysis devices has also been found to augment clinical decision-making [113].

**Other Optical Techniques**

Reflectance confocal microscopy (RCM) visualizes the epidermis and superficial dermis at the cellular level. In RCM analysis, a honeycomb epidermal pattern and densely packed, well-circumscribed dermal papillae at the dermo-epidermal junction indicate benign neoplasms, while SK-specific features include epidermal projections, keratin-filled invaginations, cords and bulbous projections, corneal pseudocysts, and a mixed vascular pattern [114–119]. In recent years, studies have identified the clinical variability of SKs and the restricted depth of imaging as challenges to accurate RCM-based diagnosis. In a retrospective analysis of 390 patients with clinically suspicious SK, dermatologists using RCM could not diagnose SK in 25% of participants [120]. SKs have previously been misdiagnosed as pigmented nevi, and RCM features have been reported as insufficient for distinguishing melanocanthoma from melanoma [121–123].

Optical coherence tomography (OCT) also provides subsurface imaging with greater penetration but lower resolution than RCM. Existing use in SK management is limited, but reported criteria for SK include acanthosis, basal hyperpigmentation, visibility of the dermo-epidermal junction, a normal honeycomb pattern, loss of normal epidermal and dermal layering, and enlarged interpapillary spaces with edged papillae [124]. Given the ability of OCT to rapidly measure architectural changes in the epidermis and dermis, this technique was also used to measure the SK clearance of a topical hydrogen peroxide solution [125]. In the future, OCT may act as an alternative or useful adjunct to histopathological examinations of SK [126].

Several experimental photodynamic techniques have been used to identify SK. A pilot trial found that autofluorescence analysis using an RBG (red, green, blue) smartphone camera under 405-nm LED excitation was able to differentiate 15 SK lesions from 36 pigmented nevi, BCC, and melanoma with high sensitivity and specificity [127]. Near-infrared autofluorescence shows that SK lesions exhibit significantly brighter emissions than normal skin [128]. Raman spectroscopy uses structural alterations in lipid proteins to distinguish melanoma from pigmented nevi, BCC, and SK, and a low-cost portable device recently achieved moderate performance in differentiating SKs and melanomas [129, 130]. Photodynamic and thermovision methods demonstrate that SK lesions have lower mean temperatures than healthy skin and that temperature gradients differ significantly between SK and BCC [131].

**Artificial Intelligence**

SK images are often used to train AI-based algorithms capable of distinguishing malignant skin tumors from benign mimics. The test dataset of the 2017 International Skin Imaging Collaboration challenge included 50 melanoma, 50 nevi, and 50 SKs, leading to the top-ranked deep learning model with an area under the receiver operating characteristic curve (AUC) of 0.954 for SKs (Fig. 3) [132].

![ISIC 2017 Challenge Winner: Diagnosis accuracy of seborrheic keratosis](image)

**Fig. 3.** Accuracy of the top-ranked algorithm from the 2017 International Skin Imaging Collaboration challenge, specific to detection of seborrheic keratoses using a 150-image dataset. The receiving operator characteristic (ROC) curve, shown in black, demonstrates sensitivity and specificity of the model. The AUC result of 0.954 indicates excellent performance.
Table 1. Summary of topical and traditional treatment studies in SK

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study type</th>
<th>Patients, n</th>
<th>Lesions, n</th>
<th>Complete clearance</th>
<th>Partial clearance</th>
<th>Post-treatment events</th>
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<tr>
<td><strong>Topical therapies</strong></td>
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| 40% hydrogen peroxide (A-101) | Phase IV open-label, single-group trial [163] | 41 | 123 (3 per patient) | 90.2% of lesions (113 days) | Not reported | • 20% of patients reported 8 AEs, all were mild or moderate  
• 4 AEs were drug-related and included discomfort at the administration site  
• 95% of patients reported “at least moderately” satisfied |
| Nitric-zinc solutions [153, 154] | Proof of concept | 15 | 50 | 74% of lesions (8 weeks) | 26% of lesions (8 weeks) | Slight, transient erythema |
| Nitric-zinc solutions [153, 154] | Interventional | 59 | 32 | 80% of lesions (6 months) | 13.3% of lesions (6 months) | Minimal pain, itching, burning |
| TCA/formic acid [153] | Phase I/II clinical trial | 60 | ≥60 | 90% of patients (180 days) | 7% of patients (180 days) | • Slight erythema  
• Reports of burning, bleeding, scales/crust, edema  
• 1 patient reported severe erythema  
• 6 patients reported drug-related AEs  
• 4 patients lost to follow-up |
| TCA focal peel [156] | Proof of concept | 23 | Not reported | 57% of patients (6 months) | 39% of patients (6 months) | Mild erythema  
78% reported “absolute satisfaction” |
| Tazarotene 0.1% cream [157] | Pilot (nonrandomized, open label) | 15 | 30 (2 per patient) | 47% of patients (6 months) | Not reported | • Burning, pruritus, and redness in 10 patients; tolerance developed |
| 12% ammonium lactate lotion [158] | Double-blind, paired comparison | 56 | 45 | 4% of lesions (16 weeks) | 41% of lesions (16 weeks) | Only lesion elevation reduced |
| **Traditional therapies** |            |             |            |                    |                   |                       |
| Cryosurgery (liquid nitrogen) | Pilot (nonrandomized, open label) [157] | 15 | 15 (1 per patient) | 100% of patients (6 months) | Not reported | • No scarring or recurrence |
| | Pilot (randomized) [164] | 18 | 18 (1 per patient) | Not reported | 100% of patients (6 weeks and >12 months) | Mean 0–10 ratings for cosmesis at 6 weeks/>12 months were 8.58/9.33 for cryotherapy and 8.28/9.39 for curettage (p > 0.05)  
• At >12 months, 61% patients preferred cryotherapy to curettage  
• 7 subjects lost to follow-up |
| Curettage (No. 15 scalpel) | Pilot (randomized) [164] | 18 | 18 (1 per patient) | Not reported | 100% of patients (6 weeks and >12 months) | • No scarring or recurrence |

AE, adverse event.
Machine- and deep learning-based systems that outperform clinician readers often include SK as a standalone category and report AUCs from 0.77 to 0.96 [133–141]. Others stratify results by increasing categories of risk and include SKs as low-risk designations [142]. Some algorithms, based on various deep learning frameworks, such as convolutional neural networks and Gabor wavelet-based learning, are trained on SK versus BCC or melanoma data only [143–146]. These computational tools show significant promise for augmenting clinical SK detection.

**Emerging Therapeutics**

Available treatments have largely been limited to destructive therapies and minor surgical techniques, including cryotherapy, shave dissection, and electrodesication and curettage [10, 41]. Many of these are not well tolerated in patients with multiple lesions and are more likely to cause postinflammatory pigmentation in skin of color [10, 147–149]. ESKATA, a 40% hydrogen peroxide topical solution and the first FDA-approved treatment for SK, was commercially discontinued in the USA in 2019 [150–152]. There is a need for more comfortable and cosmetically acceptable SK therapies.

**Topical Treatments**

Early studies of topical therapies show promise for treating SK (Table 1). Interventions of nitric-zinc solutions showed significant clearance in nearly all lesions with minimal patient discomfort and no reported relapse [153, 154]. A novel formula of trichloroacetic (TCA) and formic acid similarly showed complete response in 90% of patients, but was associated with more drug-related adverse events [155]. Focal TCA peels also showed good clinical response in darker-skinned patients (Fitzpatrick IV–V) [156]. Conversely, tazarotene 0.1% cream improved outcomes in less than half of patients, and 12% ammonium lactate lotion (Lac-Hydrin) only affected lesion elevation [157, 158]. SK clearance achieved using topical dobesilate [159], 5% imiquimod cream [160], and 3% diclofenac gel has also been reported [161]. A recent meta-analysis found no evidence for the efficacy of topical vitamin D analogues [162].

**Laser and Light-Based Therapy**

Ablative laser therapies, which can be relatively costly, have also been used to treat SK. In an observational study, carbon dioxide (CO\textsubscript{2}) laser was used for lesions that had not improved following treatment with a combination therapy of 4% hydroquinone-containing creams. Clinical improvement was scored using a subjective scale and the mean efficacy among 53 SK patients was 84% [163]. In several case series of DPN patients, the use of CO\textsubscript{2} laser treatment completely removed SK lesions without scar formation or significant discomfort [164–166]. CO\textsubscript{2} laser was also successfully used in 2 cases of irritated SK, with no evidence of recurrence at 6 and 12 months [167, 168]. Additionally, a comparative study of erbium:YAG (Er:YAG) laser and cryosurgery in 42 SK patients reported superior healing, less hyperpigmentation, and more erythema in laser-treated groups [169].

Nonablative laser therapies have also been reported. Two randomized, split-face studies comparing potassium-titanyl phosphate (KTP) laser and electrodesicication in DPN patients found that KTP treatment was comparatively effective and better-tolerated. However, post-treatment hypo- and hyperpigmentation sequelae were observed in most patients [170]. Though another prospective, investigator-blinded pilot study of pulsed dye laser (PDL) treatment in 10 DPN patients found comparative effectiveness with curettage and electrodesicication, PDL was rated the most painful of the treatment modalities and did not reduce post-treatment hyperpigmentation [148]. Another neodymium-doped:YAG (Nd:YAG) laser at 1,064 nm was successfully used to treat 2 cases of DPN with no post-treatment effects [171]. Fractional photothermolysis, intense pulsed light, and Q-switched and picosecond lasers have also been used [172–174]. Recently, the successful use of aminolevulinate photodynamic therapy (ALA-PDT) for giant SK was reported [175].

**Conclusion**

Recent advances in our understanding of immune- and oncogene-related SK pathogenesis have important implications for the treatment of both benign and neoplastic conditions. Given their ubiquity and clinical diversity, these lesions also pose an important diagnostic challenge that emphasizes their role in the development of AI-based technologies. To meet the needs of diverse patients and improve cosmetic outcomes, promising topical and laser-based treatments should be further developed.
Key Message

New therapeutic avenues and emerging topical and laser therapies could improve outcomes in SK patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Mary D. Sun made substantial contributions to the design and acquisition, analysis, and interpretation of data for this work, drafted the work, and revised it critically for important intellectual content. Allan C. Halpern made substantial contributions to the conception of the work and agrees to be accountable for all aspects of the work. Both authors provided final approval of the version to be published.
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