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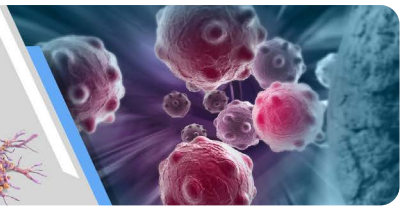

Actinic Keratosis: Current Concepts in Pathogenesis, Risk Stratification, Management, and Prevention

Running title: Pathogenesis and Management of Actinic Keratosis

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Abstract

Actinic keratosis (AK) is among the most frequently encountered premalignant skin lesions in clinical practice and is now widely regarded as part of the biologic spectrum that can progress to cutaneous squamous cell carcinoma (cSCC). The global prevalence of AK continues to increase because of aging populations, cumulative ultraviolet (UV) radiation exposure, and increasing survival of high-risk populations, highlighting its growing public health impact. Advances in molecular and cellular research have expanded the understanding of AK pathogenesis, demonstrating that chronic UV-induced DNA damage, oxidative stress, immune dysregulation, and field cancerization interact to drive the development and progression of dysplastic keratinocytes. Despite the availability of multiple lesion-directed and field-directed treatment options, management remains challenging because of disease recurrence, patient adherence, variability in treatment response, and the inability to reliably identify which lesions are most likely to progress to invasive cSCC. Emerging molecular biomarkers, genomic profiling, noninvasive imaging technologies, and novel therapeutic strategies have the potential to improve individualized risk assessment and treatment selection but require further clinical validation before widespread implementation. This critical review provides a comprehensive overview of the current understanding of AK, including its epidemiology, risk factors, pathogenesis, progression to cSCC, risk stratification, contemporary treatment approaches, barriers to effective management, preventive strategies, and future directions. Continued integration of molecular insights with patient-centered care may improve early detection, personalize therapeutic decision-making, and reduce the burden of keratinocyte carcinogenesis.

Keywords: Actinic keratosis; Chronic inflammation; Cutaneous squamous cell carcinoma; DNA damage; Genetic modification; Immune dysregulation; Keratinocytic lesion; Oxidative stress; Phenotypic susceptibility; Ultraviolet radiation

Introduction

Actinic keratosis (AK) is a common keratinocytic lesion that arises in chronically sun-damaged skin and is widely regarded as part of the disease continuum that can lead to cutaneous squamous cell carcinoma (cSCC). It is characterized by atypical proliferation of keratinocytes and clinically presents as erythematous, scaly papules or plaques [1]. Due to its high prevalence and risk of malignant progression, AK represents a major public health concern,

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especially among aging populations and regions with high cumulative UV exposure [1-3]. Recent articles describe AK as a manifestation of cumulative UV-induced field damage, often occurring within areas of chronically photodamaged skin, a concept known as field cancerization, where both visible and subclinical dysplastic abnormalities coexist [4]. This field-based nature of the disease complicates management, as treating individual lesions does not address the underlying carcinogenic environment [4]. Furthermore, the natural history of AK is not fully understood. While some lesions regress spontaneously, others persist or progress to invasive cSCC, and reliable predictors of progression at the individual lesion level are still lacking [4-8]. Despite the availability of both lesion-directed and field-directed therapies, AK management remains challenging due to variable treatment response, recurrence rates, and patient adherence [9]. More specifically, commonly used therapies such as cryotherapy demonstrate outcome variability depending on lesion characteristics and treatment technique, highlighting the need for greater standardization [9,10]. In addition, current treatment strategies are largely guided by clinical judgment rather than precise risk stratification or molecular profiling [11]. This article provides a comprehensive, critical, and up-to-date synthesis of the current understanding of actinic keratosis, including its epidemiology, risk factors, and pathogenesis, along with its progression to invasive cSCC. Further, this review will examine existing treatment modalities, barriers to effective management, and prevention strategies, while emphasizing key gaps in knowledge regarding risk prediction and limitations of current treatments.

Epidemiology and Demographics

Actinic keratosis (AK) is one of the most common dermatologic conditions encountered in clinical practice, with a growing global burden driven by aging populations and cumulative ultraviolet (UV) exposure [2]. Recent epidemiologic analyses estimate the overall prevalence of AK in the general population is 14% with a pooled incidence rate of 1,928 per 100,000 person-years [2,12]. However, reported rates vary widely depending on geographic regions, diagnostic criteria, population age structures, and study designs [13,14]. The lack of standardized diagnostic criteria across primary studies significantly limits the precision and comparability of pooled prevalence estimates, representing a major methodological limitation that remains an unresolved issue in AK epidemiologic literature [13,15,16]. Geographic variation plays a major role in AK epidemiology, with higher prevalence observed in regions near the equator and in countries with high UV radiation, including Australia and parts of Southern Europe [2,17]. These trends emphasize the central role of chronic UV exposure as a primary driver of disease development and highlight the influence of environmental and behavioral factors on disease distribution [18]. Advanced age is one of the strongest risk factors for AK, with prevalence increasing markedly in the elderly population due to cumulative UV-induced DNA damage and declining immunosurveillance capacity [19,20]. Studies consistently demonstrate that AK is considerably more common in individuals over the age of 50, with a further increase in prevalence in those of 70 years of age [21]. As populations continue to age, this trend is likely to intensify, further increasing the healthcare burden of AK and keratinocyte carcinomas [3,6-8,22-24]. Sex differences in AK prevalence have also been reported, with higher prevalence observed in males compared to females [25]. This disparity is likely attributable to higher cumulative occupational and recreational UV exposure in men along with lower use of photoprotective measures [15]. However, emerging trends suggest that these differences may be narrowing as sun protection awareness increases [16].

Fitzpatrick skin phototype is a well-established determinant of AK risk, with individuals of lighter skin types (Fitzpatrick I-II) demonstrating significantly higher susceptibility compared to those with darker pigmentation [15,26]. Melanin offers partial protection against UV-induced DNA damage, contributing to lower incidence rates in darker-skinned populations [27]. However, AK is less common in darker skin types, though the extent to which this reflects lower incidence versus underdiagnosis remains unclear [28]. Certain populations with impaired immune surveillance demonstrate disproportionately elevated rates of AK [29]. More specifically, organ transplant recipients have markedly higher rates of AK and accelerated progression to cSCC, emphasizing the role of immune function in disease control [30]. Notably, epidemiologic data are limited by heterogeneity in study methodologies, diagnostic criteria, and reporting practices. Many studies rely on clinical diagnosis without histologic confirmation, and variability in lesion counting and field assessment contribute to variable prevalence estimates [31]. These limitations highlight the need for standardized definitions and improved surveillance to accurately define disease burden and guide resource allocation.

Risk Factors and Etiology

Actinic keratosis (AK) develops through the interplay of chronic ultraviolet (UV) radiation exposure, immune dysregulation, host susceptibility factors, and the progressive accumulation of molecular alterations within epidermal keratinocytes [32]. Among these, cumulative UV radiation exposure remains the primary etiologic driver of AK development and progression [33].

Ultraviolet Radiation Exposure: The strongest environmental risk factor for AK is cumulative exposure to UV radiation [34]. Prolonged exposure to UVB wavelengths (280-320 nm) induces direct DNA damage through the formation of pyrimidine dimers and other photoproducts, while UVA radiation leads to oxidative stress and indirect

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genomic injury [35]. Repeated UV-induced damage promotes the accumulation of mutations within epidermal keratinocytes, resulting in keratinocyte dysplasia and the development of clinically apparent lesions [36]. Both recreational and occupational sun exposure contribute significantly to AK risk [37]. The association between UV exposure and AK is reflected clinically by preferential distribution of lesions on sustained sun-exposed areas, including the face, ears, scalp, dorsal hands, forearms, and neck [38]. Geographic regions with high ambient UV radiation also exhibit increased disease burden, further supporting a dose-dependent UV exposure and lesion development [2,15]. Additionally, artificial sources of UV radiation, including indoor tanning devices that are predominantly UVA-weighted, have been associated with keratinocyte carcinogenesis [39]. Given that AK represents an established precursor stage to cSCC, indoor tanning may plausibly contribute to AK formation as well, particularly among individuals with substantial lifetime exposure.

Age, skin phototype, and phenotypic susceptibility: Age is a significant determinant of AK risk because cumulative mutational burden increases over decades of UV exposure [4]. Older adults experience prolonged exposure to environmental carcinogens and exhibit age-related declines in DNA repair capacity and immune surveillance, which facilitates lesion formation [40]. Skin phototype significantly influences susceptibility to AK. Individuals with Fitzpatrick skin types I and II display a greater risk of AK than those with darker skin types due to reduced epidermal melanin content and reduced photoprotection against UV-induced DNA damage [38]. Additional phenotypic risk factors include blond or red hair, light-colored eyes, propensity to burn rather than tan, and evidence of chronic photodamage [15,18].

Genetic and Molecular Contributors: Genetic predisposition is critical in the underlying pathogenesis of several diseases [41-45]. Although UV exposure initiates the carcinogenic process, individual susceptibility to AK varies, suggesting a major contribution from genetic determinants. One of the earliest and most frequently observed molecular event is mutation of the TP53 tumor suppressor gene, which interferes with DNA damage responses and apoptosis of UV-injured keratinocytes [36,46]. Additional molecular defects associated with AK pathogenesis include abnormalities involving NOTCH signaling pathways, oxidative stress response pathways, cell-cycle regulatory genes, telomere maintenance mechanisms, and MAPK signaling pathways [46]. The progressive accumulation of these pathologic changes promotes survival and growth of atypical keratinocytes, establishing a biologic continuum between photodamaged skin, AK, and invasive cutaneous squamous cell carcinoma [47].

Environmental and Iatrogenic Factors: Additional exposures have been associated with increased AK risk. Therapeutic ultraviolet exposure, including psoralen plus ultraviolet A (PUVA) therapy, has been associated with increased rates of keratinocyte neoplasia in vulnerable individuals [48]. While less common, exposure to carcinogenic agents such as arsenic and other industrial chemicals has also been linked to the development of premalignant and malignant cutaneous lesions [49]. A personal medical history of AK, cutaneous squamous cell carcinoma, or other forms of nonmelanoma skin cancer represents another major risk factor, highlighting the additive effects of field cancerization and continuous carcinogenic exposure [50]. Individuals with several prior lesions commonly develop new lesions over time, highlighting the chronic and recurrent behavior of the disease process [50]. Taken together, these findings support a multifactorial model of AK pathogenesis in which chronic UV exposure interacts with host-specific genetic, immunologic, and phenotypic factors to drive keratinocyte dysplasia and lesion development [51]. Improved understanding of the risk factors may facilitate the identification of high-risk populations, enhance preventive interventions, and support the development of personalized risk-stratification models [51].

Progression from Actinic Keratosis to Cutaneous Squamous Cell Carcinoma

Actinic Keratosis is clinically important because it is recognized as a precursor lesion within the spectrum of keratinocytic neoplasia and is considered an early manifestation of ultraviolet-induced cutaneous squamous cell carcinoma (cSCC) [52]. Although not every AK progresses to invasive malignancy, substantial histopathologic, molecular, and clinical evidence supports a disease continuum in which a subset of lesions undergoes progressive dysplastic changes and ultimately invade beyond the epidermis into the dermis [53]. Accordingly, current clinical practice advocates treatment of AK to reduce disease burden and potentially lower the risk of malignant transformation [54]. A critical concept underlying AK progression is field cancerization, in which clinically visible lesions coexist with genetically altered but clinically unapparent keratinocytes within chronically sun-damaged skin [55]. Persistent UV exposure induces widespread DNA damage throughout the affected field, yielding multiple independent clones of atypical keratinocytes that may transform along varying biological pathways [56]. As a result, the development of cSCC reflects progression within an entire field of photodamaged skin rather than malignant transformation of a single isolated lesion [55]. Field cancerization also explains why patients frequently develop new AKs and cSCCs despite successful treatment of individual lesions [55,57].

Molecular studies further support the well-established relationship between AK and invasive cSCC. Both lesions share several genomic alterations, including mutations

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involving TP53, dysregulation of NOTCH signaling, alterations in cell-cycle control, and abnormalities affecting epidermal differentiation and inflammatory pathways [36]. More recently, transcriptomic and single-cell RNA sequencing analyses have revealed substantial similarities in gene expression profiles between AK and early invasive cSCC while demonstrating considerable molecular heterogeneity among AK lesions [36,58]. These findings suggest that malignant transformation results from the progressive accumulation of molecular alterations rather than a single transformative event. Although predicting the behavior of an individual AK lesion remains challenging, several clinical features have been consistently associated with an increased likelihood of malignant transformation. Persistent lesions or those demonstrating rapid enlargement, ulceration, induration, hyperkeratosis, or failure to respond to conventional therapy should raise concern for underlying invasive cutaneous squamous cell carcinoma (cSCC) and often justify histopathologic assessment [59,60]. Furthermore, patients with extensive field cancerization, a high burden of AK lesions, prior keratinocyte carcinomas, or chronic immunosuppression face a substantially greater overall risk of progression than individuals with isolated lesions [61,62]. Despite considerable advances in understanding AK biology, accurately identifying which individual lesions will progress to invasive cSCC and which will remain stable continues to represent a major challenge in clinical dermatology [14,51]. Current risk assessment relies primarily on clinical examination and histopathologic interpretation, both of which have limited predictive accuracy [14]. As a result, ongoing research is focused on the development of molecular biomarkers, genomic profiling, and noninvasive imaging modalities capable of improving risk stratification and allowing for more personalized management of patients with AK [51,63].

Cellular and Molecular Mechanisms

Actinic Keratosis (AK) develops when chronic ultraviolet radiation causes continuous injury to epidermal keratinocytes, resulting in DNA damage, oxidative stress, impaired apoptosis, dysregulated cell-cycle control, and clonal expansion of atypical keratinocytes [32]. Molecular studies suggest that the earliest pathogenic events associated with AK occur long before visible lesions emerge, reinforcing the concept that AK represents an early stage in the continuum of keratinocytic carcinogenesis [47] (Figure 1).

Ultraviolet Radiation and DNA Damage: Ultraviolet (UV) radiation is the primary environmental driver of AK pathogenesis, with chronic solar exposure driving the molecular events that underline keratinocyte carcinogenesis [46]. UVB radiation directly damages DNA through the formation of cyclobutane pyrimidine dimers and 6-4 photoproducts, whereas UVA promotes carcinogenesis indirectly by generating reactive oxygen species (ROS), resulting in oxidative DNA damage, protein oxidation, and lipid peroxidation [35]. Although epidermal keratinocytes possess mechanisms to repair UV-induced DNA damage, repeated UV exposure progressively exceeds its intrinsic repair capacity, allowing mutations to accumulate over time [35]. Persistent UV-induced DNA damage also produces the

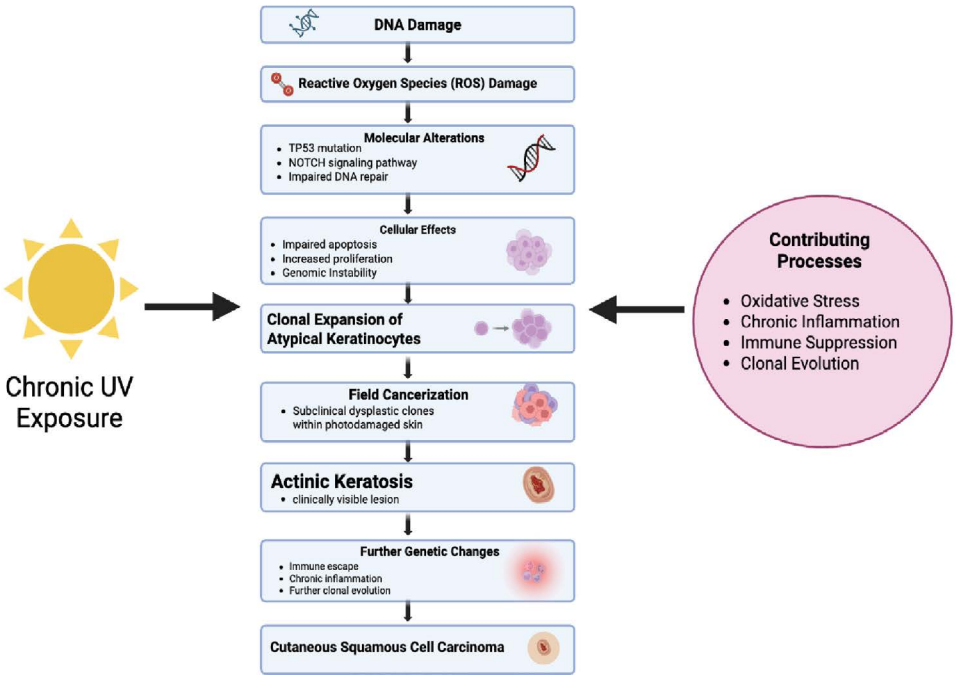

Figure 1: Molecular Pathogenesis of Actinic Keratosis.

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characteristic UV mutational profile observed in AK and cSCC, providing further evidence of their shared molecular origin [64]. As these genomic alterations accumulate, atypical keratinocyte clones multiply, creating the foundation for progressive malignant transformation [65].

Initial Genetic Modifications: The earliest and most frequent molecular event in AK development is mutation of the TP53 tumor suppressor gene. Under stable and normal conditions, the p53 protein preserves genomic stability by coordinating DNA repair, cell-cycle arrest, and apoptosis in response to DNA damage [66,67]. Ultraviolet-induced mutations in TP53 impair these protective functions, allowing for genetically damaged keratinocytes to evade apoptosis, continue proliferating, and acquire additional oncogenic alterations [68]. TP53 mutations are therefore considered one of the defining molecular hallmarks of both AK and cutaneous squamous cell carcinoma [68]. Disruption of NOTCH signaling pathways also plays an important role in AK development [69]. NOTCH signaling physiologically promotes keratinocyte differentiation while limiting excessive epidermal proliferation, thereby maintaining normal epidermal homeostasis [70]. Loss of this regulatory signaling favors the clonal expansion of atypical keratinocytes and facilitates progression toward invasive carcinoma [71]. Beyond TP53 and NOTCH, modifications involving genes that control cell-cycle progression, apoptosis, and epidermal differentiation further contribute to the biologic heterogeneity that characterize AK lesions [72].

Oxidative Stress and Chronic Inflammation: Oxidative stress and chronic inflammation result in cellular damage from unstable molecules and long-term tissue swelling, which act as core drivers in starting many long-term illnesses [73-88]. While UV exposure causes direct genomic injury, it also creates a sustained state of oxidative stress within the epidermis [89]. Reactive oxygen species (ROS) activate multiple intracellular signaling pathways that promote cellular proliferation, inflammatory mediator production, extracellular matrix remodeling, and resistance to apoptosis [80-82,89,90]. Collectively, these processes exacerbate keratinocyte dysregulation and drive progressive tissue damage [89,91]. In parallel, UV radiation establishes a chronic inflammatory microenvironment marked by increased chemokines, matrix-remodeling enzymes, and pro-inflammatory cytokines [32,92]. Continuous inflammation fuels additional DNA damage, leading to clonal selection of genetically altered keratinocytes, and enables dysplastic cell populations to expand within fields of cancerization [92]. As a result, AK is increasingly understood as a disease driven not just by accumulated mutations, but by chronic inflammatory signaling as well [92].

Immune Dysregulation and Immune Escape: Physiologically, the immune system plays a critical role in eliminating UV-induced keratinocytes, clearing them before they can undergo malignant transformation. However, persistent UV exposure perturbs this protective function by impairing cutaneous immune surveillance, including suppression of antigen presentation, reduced antitumor immune responses, and alterations in cytokine production [93,94]. Consequently, atypical keratinocyte clones evade immune-mediated clearance and persist within chronically photodamaged skin [93,94]. The lack of immune control is most pronounced in immunosuppressed patients, who exhibit elevated rates of AK development, recurrence, and progression to invasive cSCC [30,95].

Field Cancerization and Clonal Evolution: Field cancerization stands as one of the central biologic concepts underlying AK pathogenesis [96,97]. This phenomenon describes how clinically visible lesions emerge from within a broader region of sun-damaged skin that contains genetic alterations despite appearing clinically normal [97,98]. Rather than arising as isolated neoplasms, AKs develop from multiple independent clones of UV-damaged keratinocytes that compete and evolve over time and individually accumulate additional molecular changes [97]. This mechanism explains the frequent development of new lesions even after successful treatment of AKs and emphasizes the importance for field-directed therapy over treatment limited to individual lesions [98,99].

Evolving Molecular Insights: Advances in single-cell RNA sequencing and transcriptomic profiling have uncovered substantial molecular heterogeneity between different AK lesions [58,100]. Individual lesions differ in keratinocyte differentiation patterns, immune cell-infiltration, inflammatory signaling, and gene-expression profiles, indicating that AKs are not molecularly identical and differ in their risk of malignant progression [58]. These technologies have begun to identify potential biomarkers that could enhance risk stratification and encourage more personalized treatment approaches [100]. However, clinical evidence remains insufficient for routine use, and future studies are needed before molecular profiling can be integrated into standard management practices [101].

Risk Stratification

Risk stratification in actinic keratosis holds clinical value; however, it remains an unreliable practice. Current approaches cannot reliably predict whether a specific lesion will regress spontaneously, persist, or progress towards invasive cutaneous squamous cell carcinoma [1,14] (Figure 2). In the absence of that certainty, clinicians draw on a combination of factors, including features of the lesion itself, patient-specific risk factors, and overall burden of field disease, to estimate the risk of malignant progression and guide treatment approach [14]. Emerging literature suggests numerous variables associated with increased cSCC risk,

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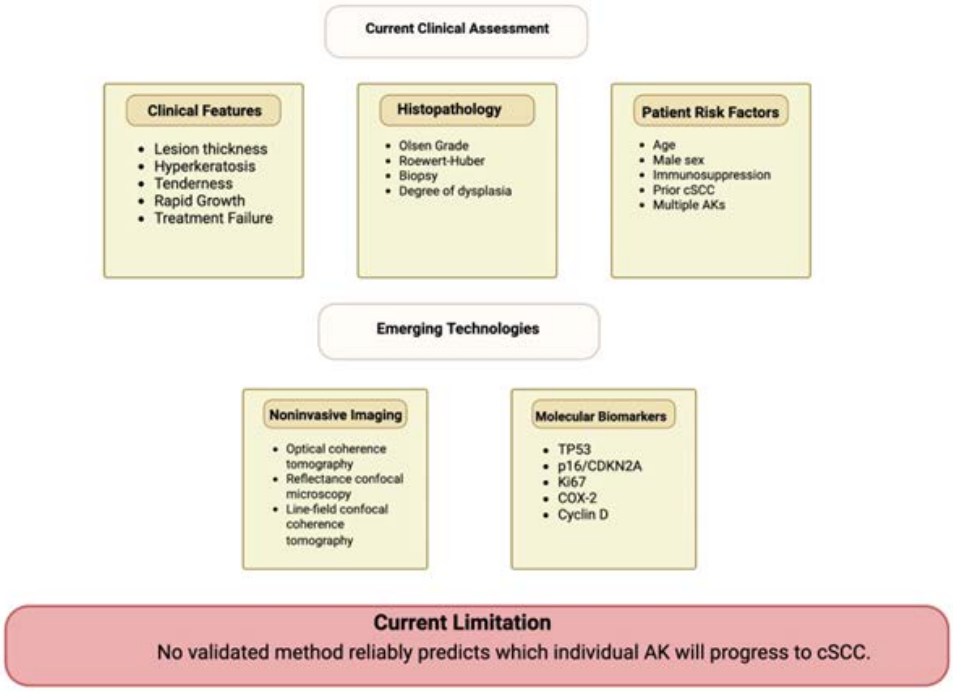

Figure 2: Progression of AK to cutaneous squamous cell carcinoma (cSCC) is influenced by multiple clinical, histopathologic, and molecular factors; however, no single method can reliably predict which individual lesions will progress to invasive disease.

including male sex, advanced age, lesion location, prior history of keratinocyte carcinoma, degree of dysplasia, and use of immunosuppressive medications [53]. However, these associations are present at the population level and do not provide lesion-specific predictions for an individual patient [21].

The Actinic Keratosis Area and Severity Index (AKASI) provide clinicians an accurate method to quantify AK severity [102]. It functions by assessing how much of the scalp, forehead, cheek, and chin areas are affected, while also accounting for distribution, thickness, and erythema [102]. Together, these factors produce a score ranging from 0 to 18 [102]. However, a comprehensive 2024 epidemiology and risk factors review identified drawbacks [21]. Both AKASI and the related AK Field Assessment Scale (AK-FAS) are time-consuming and have not yet been sufficiently evaluated in large, prospective studies for predicting cSCC risk [21]. At the individual lesion level, AKs that are thick, indurated, hyperkeratotic, tender, bleeding, rapidly growing, or resistant to treatment can indicate progression toward in situ or invasive squamous cell carcinoma [60]. Clinically, hyperkeratosis and palpability are captured using the Olsen grading scheme, which characterizes AK lesions into grades I-III [103]. Histologic grading provides further insight as well [103]. The Roewert-Huber also classifies AK lesions into grades I-III based on the vertical extent of atypical keratinocytes within the epidermis [103]. However, there is a weak correlation between Roewert-Huber histologic grade and Olsen clinical grade, suggesting that clinical grading alone should not be used to estimate histologic severity [103]. Biopsy and clinical inspection each have limitations because visible AKs represent only a portion of a larger field of UV- damaged skin, and a single biopsy cannot capture the molecular heterogeneity present throughout the entire field [97]. Patient-level risk factors are equally important to consider in risk assessment. Individuals with numerous AKs, a history of basal cell carcinoma or cutaneous squamous cell carcinoma, widespread photodamage, or chronic immunosuppression encounter a greater cumulative risk than those with isolated lesions [53,104]. Medicare also supports that an initial AK diagnosis is associated with an increased burden of skin cancer, reinforcing the perspective that AK should be treated not only as a single premalignant lesion but also as an indicator of broader carcinogenic risk [62]. Noninvasive imaging technologies represent another method to refine AK assessment [105]. Optical coherence tomography, reflectance confocal microscopy, and line-field confocal coherence tomography can visualize features pertaining to AK diagnosis, including atypical keratinocytes, parakeratosis, and disruptions in epidermal architecture [105,106]. These tools may assist in reducing unnecessary biopsies and improve treatment monitoring [106]. However, current studies indicate that standardized protocols and further clinical validation are necessary before they can influence risk stratification in daily practice [107]. In the future, developing molecular tools may enhance risk stratification. Gene-expression studies have identified UV-responsive biomarker panels that could help differentiate benign or lower-risk AKs

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from lesions with greater carcinogenic potential [108]. Some immunohistochemical biomarkers that have been identified include TP53 expression intensity, p16/CDKN2A, Ki67 proliferative index, COX-2, and Cyclin D [108]. However, these tissue or serum biomarkers have not been assessed in a prospective cohort study as a sole predictor of progression to invasive cSCC at the single lesion level [109]. Overall, AK risk stratification currently relies on integrating several factors, including clinical presentation, histologic results, patient risk factors, field cancerization, and treatment response [3]. Emerging biomarker panels and imaging technologies are demonstrating potential; however, the outstanding challenge remains the inability to reliably predict which individual lesions will progress to invasive disease [109]. This limitation supports a treatment approach centered on treating clinically important AKs, careful monitoring of high-risk patients, and additional research into imaging-based and molecular predictors of progression [3].

Current Treatments with Short-term and Long-term Outcomes

The main goals of AK treatment are to remove clinically visible lesions, minimize the extent of field cancerization, reduce symptoms, and potentially reduce the risk of progression to invasive cSCC [14]. Since there is considerable clinical and biologic heterogeneity among AK lesions, treatment should be individualized according to lesion characteristics, disease extent, patient comorbidities, patient preference, treatment tolerance, and cosmetic considerations [14]. Current management is centered around a framework distinguishing between lesion-directed therapies, which target single visible lesions, from field-directed therapies, which treat the broader area of photodamaged skin [14,104] (Figure 3). This variation in treatment carries clinical importance given the field cancerization phenomenon, where addressing only clinically apparent lesions leaves the surrounding photodamaged field preserved and susceptible to newly arising lesion formation or independent malignant transformation [97]. Current guidelines from both the American Academy of Dermatology and the European consensus group suggest personalizing treatment based on lesion count, location, clinical grade, extent of field damage, and patient immune status [14,110]. Both guidelines also recognize that patients with field cancerization generally benefit from field-directed therapy, either alone or in combination with lesion-directed treatment, rather than lesion-directed therapy alone [14,97].

Cryotherapy with liquid nitrogen remains the most widely used lesion-directed treatment for AK because of its accessibility, quick administration, and low cost for individual lesions [9,111]. This in-office procedure is performed without anesthesia, applying liquid nitrogen via a cotton-tip applicator or spray device over one to three freeze-thaw cycles [9,112]. Liquid nitrogen promotes intracellular ice

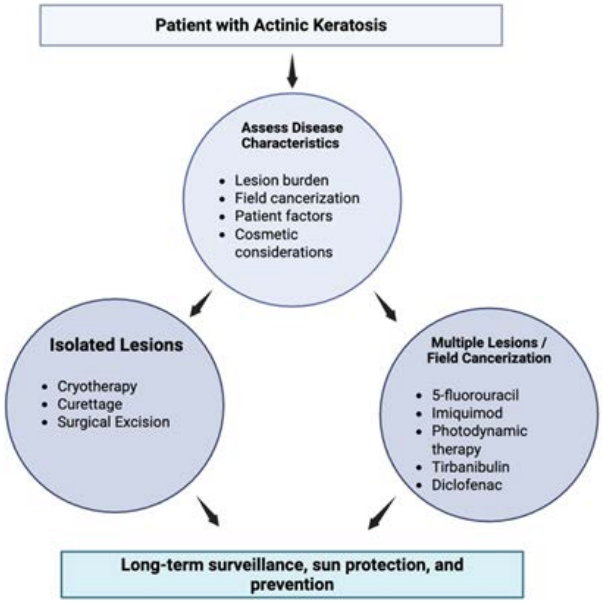

Figure 3: Management of actinic keratosis is guided by lesion burden, the presence of field cancerization, and individual patient characteristics. Patients with isolated lesions are managed with lesion-directed therapies, whereas those with multiple lesions or field cancerizations are treated with field-directed therapies. Long-term surveillance, photoprotection, and preventive strategies remain essential factors of ongoing treatment.

crystal formation, vascular injury, and subsequent destruction of atypical keratinocytes [9]. Despite its widespread use, cryotherapy is not a standardized intervention, and outcome variability represents one of its most significant limitations [52,99]. Recent clinical reviews attribute much of the variability to inconsistent freezing protocols, freeze duration, lesion thickness, operator technique, and number of freeze-thaw cycles [52]. Adverse events are mainly local, including pain, erythema, blistering, and crusting [113]. Some patients also experience permanent hypopigmentation or hyperpigmentation, specifically with longer freeze durations or in patients with Fitzpatrick phototypes III-VI [9,114]. Most importantly, cryotherapy does not address the subclinical photodamage surrounding treated lesions [99,115]. Since it only targets the clinically apparent AKs and leaves the greater field of atypical keratinocytes untouched, recurrence and de novo lesion formation in surrounding skin remain common even after successful treatment of individual lesions [99]. Therefore, patients with extensive photodamage may benefit from combining cryotherapy and field-directed treatment to improve clearance of clinically visible lesions while also addressing subclinical disease [116]. Field-directed therapies aim to treat broader areas of chronically sun-damaged skin to eliminate subclinical dysplastic keratinocytes alongside visible AKs, [117]. Topical 5-fluorouracil (5-FU) remains one of the most well-studied field therapies and is strongly recommended by current guideline support because of its

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consistent ability to reduce lesion burden and address field cancerization [117]. However, its main drawback revolves around creating local inflammatory reactions, including erythema, discomfort, crusting, and erosion, which may negatively impact adherence despite its long-term efficacy [118]. Imiquimod offers another established field-directed option that functions by activating toll-like receptor 7 and enhancing local innate and adaptive immune responses against atypical keratinocytes [119,120]. Like 5-fluorouracil, imiquimod has achieved desirable clearance rates but commonly induces local inflammatory skin reactions that can interfere with treatment completion [121]. In contrast, diclofenac sodium is generally well tolerated and associated with milder adverse effects but requires a substantially longer course of treatment and is considered less effective than other field-directed treatments [121].

Photodynamic therapy (PDT) offers another field-directed option in which a topical photosensitizing agent is activated by a particular wavelength of light, creating reactive oxygen species that selectively destroy dysplastic keratinocytes [122]. PDT is well-suited to patients with multiple facial or scalp lesions since it pairs successful field treatment with strong cosmetic outcomes [122]. However, its broader use is limited by treatment-associated pain during illumination, cost, and limited availability [122]. More recently, Tirbanibulin has emerged as a treatment option for AK [123]. This topical microtubule inhibitor is administered once daily for five consecutive days, providing a notably shorter treatment duration than many conventional field therapies [123]. Current evidence points to therapeutic efficacy, high patient satisfaction, and good tolerability, leading to a strong recommendation for its use in appropriately selected patients from the American Academy of Dermatology [54,124]. While these early results are promising, further long-term comparative studies are needed to accurately define recurrence rates, duration of response, and its role relative to established therapeutic options [54]. Growing evidence also supports sequential and combination approaches [116]. Pairing lesion-directed cryotherapy with subsequent field-directed therapy may improve overall clearance by concurrently treating subclinical disease and clinically visible lesions within the surrounding photodamaged field [116]. This strategy has demonstrated enhanced lesion reduction in selected patient populations and is increasingly considered for patients with recurrent disease or extensive field cancerization [116]. Even with numerous effective therapies available, no single treatment is optimal for all patients [121]. Variation in tolerability, efficacy, treatment duration, cosmetic outcomes, recurrence rates, cost, and adherence means clinicians must personalize management based on patient-specific factors [125]. As a result, current AK management has shifted away from a one-size-fits-all approach toward individualized treatment strategies that incorporate factors including field cancerization, lesion burden, patient preferences, and overall skin cancer risk [125].

Barriers to Early and Effective Treatment

Although numerous effective field-directed and lesion-directed therapies exist, the management of AK in daily clinical practice remains challenging. Successful treatment depends on more than efficacy of any individual therapy; it also depends on early lesion recognition, accurate assessment of field cancerization, treatment tolerability, access to care, patient adherence, and ongoing surveillance [126]. Consequently, real-world outcomes frequently differ from those reported in clinical trials, emphasizing the multiple barriers that continue to limit optimal disease management [127]. One of the most significant barriers to effective AK management is delayed recognition of disease. Since AKs are often asymptomatic and may initially appear as small or rough, many individuals dismiss their clinical significance or mistake them for chronic sun damage or normal signs of aging [114]. Further, field cancerization frequently contains numerous clinically inapparent lesions that go undetected during routine self-examination, allowing the extent of disease to be underestimated until more extensive photodamage has developed [128]. Taken together, these factors contribute to delayed presentation and emphasize the significance of patient education and frequent dermatologic assessment, especially in high-risk populations [52]. Patient adherence poses another key determinant of treatment success, specifically for field-directed therapies [126]. Topical agents such as 5-fluorouracil and imiquimod typically cause erythema, erosion, crusting, burning, and discomfort as part of their expected therapeutic response [126]. While these local skin reactions may reassure patients that the medication is exerting its intended effect, they may discourage patients from completing the full prescribed course, especially when treatment spans several weeks [129]. Systematic reviews of patient-reported outcomes repeatedly demonstrate that shorter treatment regimens and simple dosing schedules correlate with greater satisfaction and improved adherence, whereas longer treatment durations and more severe local reactions raise the likelihood of premature discontinuation [126]. The recurrent and chronic nature of AK further complicates long-term management [130]. Even after visible lesions are completely cleared, patients frequently develop new AKs within the same chronically sun-damaged skin because treatment does not eliminate the underlying carcinogenic field [55]. As a result, many patients require repeated treatment cycles and lifelong surveillance [104] . Framing AK as a chronic disease rather than a one-time problem may improve long-term engagement with preventive care and follow-up [130].

Diagnostic variability also presents a significant barrier. Distinguishing AK from hypertrophic AK, Bowen disease, and early invasive cutaneous squamous cell carcinoma can

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be clinically challenging, specifically for thicker or inflamed lesions [131]. In addition, significant variability exists in lesion counting methods, severity grading, and outcome measures used across clinical studies, making it difficult to compare results between clinical trials 25]. Recent studies have highlighted the need for standardized AK severity metrics and validated outcome measures to improve research quality and clinical decision-making [25,132]. Healthcare system factors can also influence treatment selection and outcomes. Access to dermatologic care, insurance coverage, treatment cost, medication availability, and geographic disparities in specialist access all play a role in timely diagnosis and management of AK [133]. Certain therapies, such as photodynamic therapy, may be unavailable in some practice settings or may carry higher out-of-pocket costs, prompting clinicians and patients to select alternative treatments despite differences in efficacy, tolerability, or cosmetic outcomes [134]. Given these limitations, shared decision-making becomes essential to align treatment choices with patient priorities while considering practical limitations [135]. Lastly, increasing attention has turned to patient-centered care as a means of addressing many of these barriers [136]. Clear communication regarding the chronic nature of AK, expected treatment reactions, the importance of treatment completion, and the reasoning behind field-directed therapy has been associated with enhanced patient satisfaction and stronger adherence [136]. Recent guideline recommendations further advocate for personalized treatment plans that account for patient preferences, lesion burden, cosmetic concerns, tolerance for adverse effects, and lifestyle factors, recognizing that optimal long-term management extends beyond lesion clearance alone [136,137]. Taken together, these barriers show that effective AK management requires more than selecting an effective therapy [135]. Improving patient education, adherence, access to care, diagnostic consistency, and personalized treatment strategies will be essential for reducing recurrence, enhancing long-term outcomes, and maximizing the benefits of currently available therapies [136].

Preventive Strategies

Primary Prevention: Sun Protection Behaviors: UV exposure is the dominant modifiable risk factor for AK; therefore, behavioral prevention remains the first line of defense [3,138]. Strategies that reduce cumulative UV exposure show varying degrees of effectiveness, with the strongest evidence supporting regular sunscreen use [138,139]. Regular application of broad-spectrum sunscreen significantly reduces AK incidence. The landmark Nambour Skin Cancer Prevention Trial, a randomized controlled study conducted in Australia, found that participants assigned to daily sunscreen use developed fewer new AKs and experienced regression of existing lesions compared with those using sunscreen irregularly [140-142]. This provides direct evidence that consistent sunscreen use not only prevents sunburn but also reduces UV-induced precancerous lesions [138,142]. Sunscreen protection also increases with SPF level. SPF 15 blocks approximately 93% of UVB rays, SPF 30 blocks about 97%, and SPF 50 blocks roughly 98% [139]. Because most people apply sunscreen at less than half the recommended thickness, a higher labeled SPF helps compensate for underapplication in real-world use [139,143]. Physical barriers complement sunscreen and can be highly effective. UPF-rated clothing blocks a substantial proportion of UV radiation. Under the Australian and New Zealand Standard, UPF 15-24 garments block 93.3 to 95.9% of UVB, UPF 25 to 50 garments block 96.0 to 98.9%, and UPF 50+ garments block 99% or more [144]. Wide-brimmed hats also meaningfully reduce UV exposure to high-risk facial zones. In a modeling study, Backes et al. found that a wide-brimmed hat reduced mean facial UV dose by half compared with no hat (1.7 SED vs 3.3 SED) during cloudless summer midday conditions, with the greatest protection observed at the nose, eyes, and ears [145]. Hats with circular brims also reduced neck exposure during summer months [145]. However, no hat style achieved complete protection at any facial zone, with a maximum protection factor of 76%, and effectiveness varied considerably with sun angle and environmental conditions [145]. The CDC therefore recommends a hat with a circumferential brim of at least 3 inches that shades the face, neck, and ears, and advises against relying on standard baseball caps alone [146]. Fewer studies have directly examined clothing in relation to AK incidence specifically, but the established UV-blocking effectiveness of these physical barriers supports a biologically plausible role in reducing cumulative photodamage and lesion formation [139,140]. Clothing also offers a practical advantage over topical products because it does not require reapplication and may reduce dependence on repeated sunscreen use, making it a comparatively accessible option for patients facing socioeconomic barriers or physical limitations that complicate frequent sunscreen application [144]. At the population level, public health initiatives have demonstrated that sustained sun-protection messaging can shift behavior and reduce UV-related skin disease. Australia's SunSmart campaign provides the clearest example. Long-term evaluation has shown sustained increases in sunscreen use, hat wearing, and shade seeking, alongside reduced sunburn prevalence and favorable skin cancer incidence trends among younger populations [147-149]. The campaign has been associated with decreased melanoma incidence among Australians under 55 years of age, and economic modeling estimates it has prevented thousands of skin cancers and saved substantial healthcare costs [150,151]. These findings show the real-world effectiveness of coordinated prevention strategies [152,153]. Despite the demonstrated effectiveness of these measures, their real-world impact depends on consistent, sustained adherence. Primary prevention reduces AK burden

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only when protective behaviors are maintained over time, making adherence a key consideration and highlighting the importance of understanding the barriers that may limit engagement with preventive strategies.

Secondary Prevention: Once individuals are at increased risk of actinic keratosis (AK) or have already developed lesions, the focus of prevention shifts from primary prevention to secondary prevention. AKs develop in chronically sun-damaged skin, so secondary prevention focuses on identifying lesions that may progress to cancer and reducing the amount of precancerous tissue. Total body skin examinations (TBSEs) are important to surveillance in individuals at elevated risk of keratinocyte carcinoma. High-risk groups include organ transplant recipients receiving long-term immunosuppression, individuals with a history of non-melanoma skin cancer, patients with extensive actinic damage or multiple AKs, and those with fair skin phototypes who have accumulated substantial lifetime UV exposure 154,155]. Professional organizations recommend regular dermatologic surveillance for these populations. For example, transplant dermatology guidelines often recommend at least annual skin examinations, with more frequent reviews for patients who have previously developed skin cancer or numerous Aks [156,157]. Similarly, patients with a history of cutaneous squamous cell carcinoma (cSCC) are commonly reviewed every 3-12 months depending on recurrence risk and disease burden [154]. Despite widespread clinical adoption, there is no direct evidence that routine skin cancer screening reduces cSCC-specific mortality, as there has not been a study to report this as an outcome measure [158]. This same notion holds true for melanoma as well, where more research has been conducted, yet the available evidence remains insufficient to demonstrate a clear mortality benefit [159]. No such randomized controlled trials have been completed [160]. A significant portion of the available evidence has come from German population screening programs and other observational studies. These studies reported an initial reduction in mortality, but this effect was not maintained during longer follow-up [158]. Given the relatively low mortality associated with cSCC and the logistical challenges of conducting large screening trials, definitive evidence of a mortality benefit remains difficult to obtain [159]. This represents an important gap in the literature and highlights the need for further research evaluating the efficacy and cost-effectiveness of skin cancer screening programs. Self-skin examination provides an additional opportunity for early detection between clinical visits. Patients can be taught to monitor existing lesions for changes in size, thickness, tenderness, or failure to heal, while also identifying newly emerging lesions within sun-damaged skin [155]. Studies suggest that patient-performed examinations can improve the detection of suspicious lesions, particularly when combined with educational interventions. However, diagnostic accuracy is variable and generally lower than that of trained clinicians. Accordingly, self-skin examination is encouraged as an adjunct to regular clinical surveillance, rather than serving as a replacement. Beyond surveillance, chemoprevention seeks to reduce the development of new AKs and keratinocyte carcinomas through pharmacological intervention. Oral retinoids are among the most extensively studied agents, particularly in immunosuppressed populations. By promoting normal keratinocyte differentiation and inhibiting epidermal proliferation, retinoids may reduce the formation of premalignant and malignant lesions [161]. Clinical trials in organ transplant recipients have demonstrated significant reductions in the incidence of new AKs and cSCCs during treatment with systemic retinoids such as acitretin [162,163]. However, these benefits often diminish following treatment discontinuation, and long-term use is frequently limited by adverse effects including mucocutaneous dryness, hepatotoxicity, dyslipidemia, and teratogenicity [161,164]. Consequently, oral retinoids are generally reserved for patients at exceptionally high risk of recurrent skin cancer rather than for routine prevention in the general population [155,157]. Nicotinamide has emerged as a promising chemopreventive agent because of its favorable safety profile. Ultraviolet radiation depletes cellular energy stores and impairs DNA repair and cutaneous immune function. Nicotinamide replenishes intracellular nicotinamide adenine dinucleotide (NAD^+) levels, thereby supporting DNA repair mechanisms and reducing UV-induced immunosuppression [165]. The phase III ONTRAC trial demonstrated that oral nicotinamide 500 mg twice daily, reduced the incidence of new non-melanoma skin cancers by approximately 23% and the number of AKs in high-risk individuals over 12 months [166]. Notably, these benefits were observed only during active treatment, with protection diminishing after cessation [166,167]. However, nicotinamide's low cost, favorable tolerability, and ease of administration have made it an attractive option for secondary prevention in high-risk patients [164,167,168].

Topical field-directed therapies, including 5-fluorouracil, imiquimod, and photodynamic therapy, also reduce the burden of clinically visible and subclinical AKs within chronically sun-damaged skin [3,166]. Although these therapies are primarily used to treat existing lesions rather than prevent their initial development, they reduce the number of precancerous changes within chronically sun-damaged skin by eliminating dysplastic keratinocytes that may give rise to future lesions [154]. Together, surveillance and chemoprevention form the foundation of secondary prevention for AK. Regular skin examinations facilitate earlier detection of malignant change, while pharmacological interventions may reduce lesion burden and the risk of future carcinoma. There are still uncertainties regarding optimal surveillance intervals, long-term chemoprevention strategies, and the extent these

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approaches reduce cSCC-related morbidity and mortality. Future research should aim to clarify these uncertainties and identify the most effective and cost-effective approaches to secondary prevention in high-risk populations.

Gaps in Our Knowledge and Future Directions

Current treatment approaches for actinic keratosis face several important limitations that restrict their long-term effectiveness. Therapies such as topical 5-fluorouracil, imiquimod, and photodynamic therapy address subclinical lesions across an area of sun-damaged skin, but they are often limited by poor patient adherence due to significant local skin reactions [50]. These skin reactions include erythema, crusting, and discomfort, which can lead patients to discontinue treatment before completing the full course. Lesion-directed therapies like cryotherapy are quick and convenient but only treat clinically visible lesions, leaving the subclinical UV damage untreated. This dilemma is the main reason why AK recurrence rates remain high. AK is not an isolated lesion but a visible manifestation of a larger area of cumulative photodamage called "field cancerization," in which keratinocytes through repeated sun-exposure are genetically mutated before any lesion becomes clinically apparent [50]. Treating only the visible lesion does not address the surrounding subclinical field, so new lesions frequently emerge from adjacent damaged tissue rather than representing true treatment failure of the original lesion. Ongoing UV exposure, incomplete patient adherence to field therapies, immunosuppression, and the difficulty of achieving complete microscopic clearance (as opposed to just clinical clearance) all contribute to recurrence [50]. Together, these factors mean that no current therapy offers a durable cure, and management is better understood as long-term suppression of a chronic, field-wide process rather than a one-time eradication.

Despite decades of research, the natural history of actinic keratosis remains poorly understood at the individual level, which limits clinician's ability to predict which lesions will progress to invasive squamous cell carcinoma, which will persist unchanged, and which will spontaneously regress [50]. Published estimates of malignant transformation rates per lesion vary enormously, from well under 1% to over 20% depending on the study population and follow-up duration [50,169], reflecting the absence of a reliable biomarker or histological feature that can prospectively distinguish a stable AK from one with a trajectory toward malignancy. Current grading systems, such as the Olsen clinical grading scale and the AK/SCC histological continuum, attempt to stratify risk based on morphology and degree of atypical cells, but neither has been validated as a strong independent predictor of progression, and inter-rater reliability remains inconsistent. It is also unclear why some patients with extensive field cancerization never develop invasive disease while others with a single lesion progress relatively quickly, suggesting that individual factors such as immune surveillance, genetic susceptibility, and local microenvironment likely play a role that is not yet well characterized. Molecular work has identified recurrent mutations in genes like TP53 and CDKN2A in AK lesions, but these same mutations are common in normal sun-exposed skin, so their presence cannot explain why only a minority of AKs progress. This uncertainty has direct clinical consequences, since it makes it difficult to counsel patients on individualized risk and complicates whether all AKs need treatment or whether a watchful-waiting approach is appropriate for lower-risk lesions. Longitudinal cohort studies with standardized grading and molecular correlations are needed to build risk-prediction models that go beyond population-level averages. Emerging treatment strategies for actinic keratosis are moving in two directions. One is to enhance the immune response against dysplastic keratinocytes, and the other is directly targeting the molecular pathways that drive their proliferation and survival [144] . On the immunotherapy side, agents such as resiquimod, ingenol disoxate, and topical anti-PD1 formulations are under investigation, building on the immune-modulating mechanism already established by imiquimod [170]. Resiquimod, for example, acts as a topical immune modifier that engages TLR7/8, activating myeloid and other immune cells to drive clearance of dysplastic tissue [170]. This approach amplifies the same innate and adaptive immune surveillance thought to underlie spontaneous AK regression. This immune-based strategy carries a limitation as their efficacy is somewhat reduced in solid organ transplant recipients because of their immunosuppressed state [170]. On the targeted molecular therapy side, investigation agents that act on specific pathways implicated in keratinocyte dysplasia are being explored. These include EGFR/ErbB2 antagonists such as sinecatechins, beta-tubulin antagonists such as paclitaxel, Na+/K+-ATPase inhibitors such as furosemide and digoxin, and VDAC/hexokinase 2 modulators such as tuvatexib [170]. These work to disrupt the specific proliferative or metabolic machinery of dysplastic cells rather than relying on the host immune system to do so. Combination approaches are also being tested clinically, such as pairing topical calcipotriene, a vitamin D analog with immunomodulatory effects, with 5-fluorouracil to enhance field treatment, particularly in high-risk populations like organ transplant recipients. Overall immunotherapy approaches engage the body's own surveillance mechanisms but are restricted in immunosuppressed patients. Targeted molecular therapies bypass the need for intact immune function but require more precise understanding of the pathways driving individual lesions. This gap connects directly to the unresolved questions around the risk prediction in individual patients. Further research and clinical trials will clarify how these approaches

fit into the evolving knowledge of AK management. A major research priority in AK is the development of non-invasive, biopsy-free methods that can distinguish stable lesions from malignant risk lesions. Since it is currently not possible to determine which AK lesions are at higher risk of progressing to SCC [169], and the biopsy required to assess histology is invasive, costly, and impractical to perform across every lesion in a field of multiple AKs, a biopsy-free method is needed. A developing approach uses adhesive tape stripping to non-invasively collect epidermal RNA for gene expression profiling [169]. It can identify differentially expressed genes that may play a role in AK progression to SCC, potentially opening a path toward biopsy-free genomic risk stratification [169]. In parallel, imaging-based biomarkers are advancing as complementary tools, including reflectance confocal microscopy (RCM), line-field confocal optical coherence tomography, and high-frequency ultrasound, which allow in vivo visualization of epidermal disorganization, keratinocyte atypia, and dermal remodeling that would only be visible on histology [171]. RCM has proven useful for characterizing field cancerization. It can reveal an atypical honeycomb pattern within the granular and spinous layers in subclinical AK that is not yet visible to the naked eye, a way to map the extent of a patient's photodamaged field beyond what clinical exam alone can detect. This matters clinically because clinical clearance after therapies does not correspond to histological resolution, which results in subclinical persistence and risk of recurrence [171]. Imaging-based monitoring could eventually help clinicians confirm true histological clearance rather than relying on visual assessment alone. Together, these non-invasive biomarker strategies, spanning genomic, cellular, and structural levels, are a critical piece needed to move AK risk prediction from population-level toward individualized, mechanism-based decision-making.

Key Points

- Actinic Keratosis is one of the most common premalignant skin lesions and represents an early stage in the continuum leading to cutaneous squamous cell carcinoma.
- Chronic ultraviolet radiation exposure remains the primary driver of AK development through cumulative DNA damage, oxidative stress, immune dysregulation, and clonal expansion of atypical keratinocytes.
- Field cancerization is a fundamental concept in AK pathogenesis and helps explain the frequent recurrence of lesions despite successful treatment of individual AKs.
- Current risk stratification relies largely on clinical assessment because validated biomarkers capable of predicting progression of individual lesions are not yet available.
- Lesion-directed therapies target clinically apparent AKs, whereas field-directed therapies treat both visible and subclinical lesions within areas of chronically sun-damaged skin.
- Management should be individualized according to lesion characteristics, the extent of field disease, patient comorbidities, treatment tolerability, and patient preferences, as no single therapy is appropriate for all patients.
- Patient adherence, delayed lesion recognition, limited access to care, and variability in disease assessment continue to represent significant barriers to effective long-term management.
- Primary prevention through comprehensive photoprotection and secondary prevention through surveillance and appropriate chemoprevention remain essential components of AK management.
- Emerging molecular biomarkers, genomic profiling, and advanced noninvasive imaging modalities have the potential to improve individualized risk prediction and guide more personalized treatment strategies.
- Future research should focus on improving prediction of malignant progression, optimization of field-directed therapies, and development of durable treatment strategies capable of reducing recurrence and preventing progression to cutaneous squamous cell carcinoma.

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Consent for publication

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