

Photodynamic Diagnosis of Actinic Keratosis: A Systematic Review

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Actinic keratosis is a precancerous condition typically diagnosed by hyperkeratotic papules. The concept of field cancerization suggests subclinical lesions surround visible actinic keratoses. Photodynamic diagnosis is a noninvasive imaging modality that can improve actinic keratosis diagnosis and treatment assessment. This systematic review describes current evidence regarding photodynamic diagnosis modalities for actinic keratosis. We searched MEDLINE and Embase through 28 February 2025. Data synthesis was descriptive due to methodological heterogeneity across studies. Thirty-seven studies were included. Methyl aminolevulinic acid were used in 54% and 51% of studies, respectively. Incubation times ranged from 20 to 1080 min, 70% of studies followed a 3-h protocol. Most excitation sources (89%) emitted light within the 400–410 nm range, often via clinical-grade systems (54%). Imaging hardware varied: 54% used integrated clinical systems, 30% used independent cameras. Fluorescence quantification was described in 62% of studies, and 54% used specialized analysis software. Patient positioning was rarely reported (8%). This review highlights significant methodological heterogeneity in actinic keratosis photodynamic diagnosis, particularly in photosensitizer protocols and imaging systems. While clinical-grade systems provide standardization, low-cost alternatives enhance accessibility. However, lack of procedural consistency limits comparability. Future efforts should focus on advancing standardized protocols to support broader clinical validation and adoption.

Key words: actinic keratosis; photodiagnosis; photodynamic therapy; protoporphyrin IX.

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Actinic keratosis (AK) is a common precancerous skin condition induced by repeated ultraviolet

SIGNIFICANCE

Actinic keratosis is a precancerous skin condition that develops on chronically sun-exposed skin. It can be challenging to identify the full extent of actinic keratoses because some lesions are barely visible. Photodynamic diagnosis – a light-based imaging technique – helps spot these hidden lesions and assess treatment success. We reviewed published studies to see if common protocols exist for photodynamic diagnosis and how to move towards a standardized approach. While studies shared show similarities, we found major variations in how photodynamic diagnosis was conducted, making it difficult to directly compare results across studies.

(UV) exposure, and thus typically developing on sun-exposed areas such as the face, scalp and dorsal hands (1–3). Established risk factors include cumulative UV exposure, advanced age, fair skin (Fitzpatrick phototypes I–II) and immunosuppression (4–6). AK represents the visible manifestation of a broader subclinical process known as field cancerization, in which seemingly normal perilesional skin also harbours UV-induced molecular damage (7, 8). Contemporary management therefore targets both the clinically apparent lesions and the surrounding field to achieve durable remission and reduce recurrence.

While many AKs remain stable or regress spontaneously, a small proportion may progress to invasive cutaneous squamous cell carcinoma (cSCC). Reported annual transformation rates ranged from 0.025% to 16% over follow-up periods of 1–10 years in a review of 5 studies by Glogau et al. (9). The variability of this rate could be explained by several factors such as differences in the patients' age across studies, the severity of AK and the extent of field cancerization. Indeed, transformation risk rises with the number of lesions and the extent of field cancerization, highlighting the importance of field-directed therapeutic strategies (10).

Several noninvasive imaging modalities enable the visualization of the subclinical disease and thus the delineation of the limits of the field cancerization. Dermoscopy enhances diagnostic accuracy and correlates well with histopathological findings (11). Reflectance confocal microscopy (RCM) offers

near-histological resolution *in vivo* and can detect microscopic changes before they are clinically evident (12, 13). Optical coherence tomography (OCT) is valuable for early identification of keratinocytic neoplasia (14, 15). Line-field confocal optical coherence tomography (LC-OCT) provides high resolution and horizontal, vertical and 3-dimensional section images (16) that can be used for monitoring the efficacy of various treatments (17). Nonetheless, dermoscopy, RCM, OCT and LC-OCT can assess only a limited field of view at a time ($<1\text{ cm}^2$), and they only provide anatomical information but not functional insights. Among the imaging modalities, fluorescence-based photodynamic diagnosis (PDD) is the only one that offers such functional assessment and can evaluate a whole field cancerization at once.

After topical application, aminolevulinic acid (ALA) or methyl-aminolevulinate (MAL) enters the cells, where it is metabolized to the photosensitizer protoporphyrin IX (PpIX). Due to alterations in several cellular mechanisms (heme biosynthesis, mitochondrial functions, PpIX efflux, etc.), the metabolized PpIX accumulates in the dysplastic keratinocytes up to 4 times more compared to healthy cells (18). This preferential accumulation is the basis for selective fluorescence detection of dysplastic keratinocytes, commonly referred to as photodynamic diagnosis (PDD), a companion procedure to photodynamic therapy (PDT), a commonly used treatment for AK. In fact, under blue light (400–410 nm), PpIX emits visible red fluorescence (600–700 nm) (19), that enables real-time visualization of both clinical and subclinical lesions (20–22). This fluorescence results from the return of PpIX to ground state after excitation by the blue light.

The first descriptions of PDD for AK followed the development of PDT with ALA in the 1990s (23, 24). The objective was to assess *in vivo* PpIX production after incubation with ALA. A Wood's lamp emitting ultraviolet light was applied to induce PpIX fluorescence and the qualitative assessment of this fluorescence was used to predict sensibility to PDT. This simple technique is still used nowadays but, as subsequently established by the present manuscript, more sophisticated methods have been recently developed to optimize PDD. Since these early applications, the methodology of PDD has progressively evolved with the development of more advanced and quantitative technologies. Several clinical trials, including some reported in the present review, have used PDD to assess AK treatments; however, no gold standard for this technique has yet been established.

This is to our knowledge the first systematic review that aims to summarize current evidence on PDD for AK and field cancerization, discuss technical

considerations, and explore its potential integration into clinical practice.

MATERIALS AND METHODS

Search strategy and selection criteria

A comprehensive search of the MEDLINE and Embase databases was performed from their inception to 28 February 2025. The search used the following terms: (“fluorescence” OR “fluorescent”) AND (“actinic keratosis” OR “actinic keratoses”). The following MeSH terms were also used to try to broaden the search: “keratosis, actinic” [MeSH Terms], “photochemotherapy” [MeSH Terms], “aminolevulinic acid” [MeSH Terms], “skin neoplasms” [MeSH Terms], “fluorescence” [MeSH Terms]. Only articles in English were included.

Screening and data extraction

Two independent reviewers screened titles and abstracts, evaluated full texts for eligibility, and extracted data using a dedicated data extraction sheet. Discrepancies were resolved by consensus.

Inclusion criteria

The following inclusion criteria were applied for this review: human studies involving AK or field cancerization assessed with PpIX fluorescence and English articles.

Exclusion criteria

Ex-vivo studies, nonhuman studies, reviews and conference abstracts without full text were excluded from this review. The articles in which fluorescence was not assessed via imaging techniques (e.g.) studies that used spectroscopy probes only) were also excluded.

Data items

The following data were collected from the selected articles: precursor type and concentration, incubation parameters, standardization of the patient's position, illumination system (light source, excitation wavelength), acquisition system (camera...), image treatment and fluorescence assessment.

PRISMA compliance

The review adheres to PRISMA 2020. A completed checklist is provided in Appendix S1. This review was not registered, and no protocol was prepared, as the intended descriptive synthesis did not involve statistical analyses requiring predefined analytical methods.

Data synthesis

Given the substantial methodological heterogeneity across studies — particularly in photosensitizer precursor concentration, incubation time, excitation wavelength, imaging hardware and data presentation — no quantitative meta-analysis could be performed. Instead, we calculated proportions to characterize how frequently specific technical choices were reported ((e.g.) percentage of studies using MAL vs ALA vs both, percentage of studies for each incubation time, percentage of studies including calibration methods). Continuous variables are summarized descriptively.

RESULTS

Study selection

A total of 324 records were originally identified through systematic database searching; after removing duplicates (94) and applying automation tools (“article” and “letter” filter on EMBASE), 140 titles and abstracts were screened. Thirty-seven full-text articles were appropriate for inclusion (PRISMA flow-chart, **Fig. 1**) (24–58). No previous review was found.

The data collection form is provided in **Table I** and data items are summarized in **Fig. 2**.

Overview of techniques reported

–**Photosensitizer:** MAL was used in 54% of studies and ALA in 51% (some studies reported the use of both photosensitizers (5%)).

–**Incubation time:** Reported incubation time ranged from 20 to 1,080 min. A 3 h incubation time was used in 70% of studies, which is the recommended incubation time for conventional PDT with most of the currently commercially available PpIX precursors.

–**Excitation source:** More than 54 % of the light sources used were clinical-grade fluorescence systems: the Dyaderm system (Biocam GmbH, Regensburg, Germany) (30%), the Medeikonos system (Medeikonos AB, Gothenburg, Sweden) (19%) and the FotoFinder dermoscope system (FotoFinder Systems GmbH, Bad Birnbach, Germany) (5%); other light sources included Wood’s lamp (16%), UV dermoscope DermLite DL5 (DermLiteLLC, Aliso Viejo) (3%) or another kind of blue lamp (LEDs or other) (27%). Among articles that reported spectral information on the light source (73%), the central wavelength was between 400 and 410 nm in 89%, 365 nm in 7% and 442 nm in 4%. **Fig. 3**.

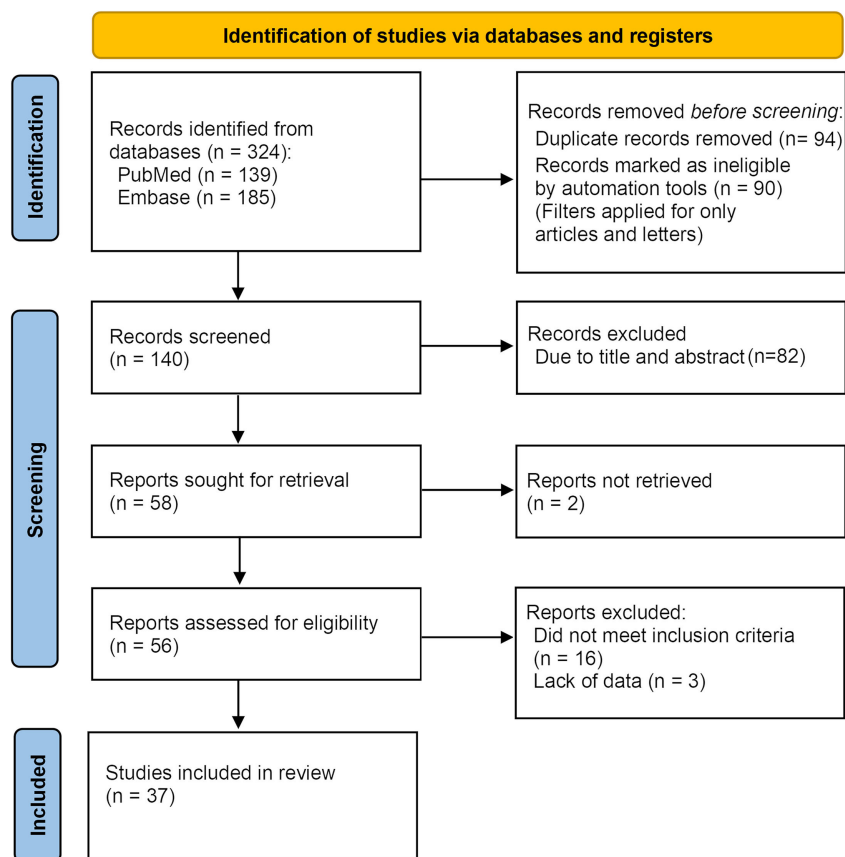


Fig. 1. PRISMA flow chart. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram representing the process of identifying, screening, and selecting studies for the systematic review.

Table I. Extracted data in studies on PDD of AK

Author (Year)	Photosensitizer (type, concentration)	Incubation (min)	Excitation λ (nm)	Imaging device	Fluorescence assessment	Standardization of the patient's position
Smits T et al. (2005)	5-ALA20%	3 h	407 nm	Dyaderm system	Arbitrary units using ImageJ software	NA
Smits T et al. (2007)	5-ALA20%	3 h	370–440 nm	Dyaderm system	Arbitrary units using ImageJ software	NA
Fauteck JD et al. (2008)	5-ALA(patch, 2 mg/cm ²)	2 to 5 h	370–440 nm	Dyaderm system	Relative fluorescence intensity	NA
Kleinpenning MM et al. (2010)	MAL	3 h	370–440 nm	Dyaderm system	Quantification (not detailed)	NA
de Leeuw J et al. (2009)	5-ALA (liposomal)	2.5 h ^a	405 nm	Dyaderm system	Fluorescence scale from green to red automatically provided by the computer	NA
Tyrrell J et al. (2010)	MAL16%	3 h	370–440 nm	Dyaderm system	Arbitrary units using ImageJ software	NA
Tyrrell JS et al. (2010)	MAL16%	3 h	407 nm	Dyaderm system	Arbitrary units using ImageJ software	NA
Tyrrell JS et al. (2011)	MAL16%	3 h	407 nm	Dyaderm system	Arbitrary units using ImageJ software	NA
Blake E et al. (2013)	MAL16%	3 h	370–440 nm	Dyaderm system	Arbitrary units using ImageJ software	NA
Tyrrell J et al. (2019)	MAL16%	3 h	370–440 nm	Dyaderm system	Arbitrary units using ImageJ software	NA
Wiegell SR et al. (2008)	MAL16%	3 h	365 And 405 nm	Medeikonos system	Calibration using a fluorescence standard: arbitrary units (AU)	NA
Wiegell SR et al. (2009)	MAL16%	3 h	365 and 405 nm	Medeikonos system	Arbitrary units using matlab program and calibration standard	NA
Togsverd-Bo et al. (2012)	MAL16%	3 h	365 and 405 nm	Medeikonos system	Calibration using a fluorescence standard: arbitrary units (AU)	NA
Petersen B et al. (2014)	MAL16%	3 h	365 and 405 nm	Medeikonos system	Arbitrary units using matlab program and calibration standard	NA
Wiegell SR et al. (2014)	MAL16%	3 h	365 and 405 nm	Medeikonos system	Arbitrary units using matlab program and calibration standard	NA
Wiegell SR et al. (2016)	MAL16%	30 min to 3 h	365 and 405 nm	Medeikonos system	Calibration using a fluorescence standard. arbitrary units (AU)	NA
Rossi A et al. (2016)	MAL16%	100–120 min	340–420 nm	FotoFinder system	Manual grading of fluorescence intensity+extension of fluorescence	Distance of 10 cm from the skin
Bartosńska J et al. (2022)	5-ALA	3 h	Not stated	FotoFinder system	Manual grading of fluorescence intensity and distribution of fluorescence	NA
Szeimies RM et al. (2002)	5-ALA20%	4 h	365 and 405 nm	Camera	Relative fluorescence intensity	NA
Ericson et al. (2004)	5-ALA20%	3 h	365 and 405 nm	Camera	Fluorescence relative units using reference markers	NA
Sieroń A et al. (2004)	5-ALA20%	10 h	442 nm	Camera	Presence or absence of fluorescence	NA
Puizina-Ivić N et al. (2008)	5-ALA20%	5 h	405 nm	Camera	Manual grading of fluorescence intensity	NA
Ortonne JP et al. (2010)	MAL (concentration not provided)	3 h	Not stated	Camera	Count of fluorescent lesions	Same position and distance. Previous photograph was used to orientate subject and camera.
Van der Beek N et al. (2012)	5-ALA (liposomal) (concentration not provided)	2.5 h ^a	407 nm	Camera	Non-normalized and normalized PpIX fluorescence relative to the auto-fluorescence	NA
Neittaanmäki-Perttu N et al. (2013)	MAL16%	3–4 h	NA	Camera	Delimitation of the fluorescence	NA
Piffaretti F et al. (2013)	MAL16%	3 h	Not stated	Camera	Mean fluorescence intensity of using a reference fluorescing spot. arbitrary units (AU)	Device's orientation and angle with respect to the lesion precisely defined and kept constant for each fluorescent measurement
Kulyk O et al. (2015)	MAL16% or 5-ALA10%	3 h	405 nm	Camera	Arbitrary units using matlab program	NA
Kim BK et al. (2015)	MAL16%	3 h	365 nm	Camera	Count of fluorescent lesions	UV lamp at 11 cm from the skin
Bobyry I et al. (2019)	5-ALA20%	3 h	NA	Camera	Gradation of fluorescence intensity from 0 to 255	NA
Willey A et al. (2019)	5-ALA20%	20 min (+skin heating)	403–432 nm	Camera	Scale of 0 to 255 using Image Pro analysis software	NA
Li L et al. (2024)	5-ALA20%	3 h	385–405 nm	Camera	Manual grading of fluorescence intensity+field cancerization delimitation using ImageJ colour histogram	NA
Fernández-Guarino M et al. (2020)	MAL16% or 5-ALA10%	2 h	NA	Smartphone	No	NA
Korecka et al. (2024)	5-ALA10%	3 h	365 nm	Smartphone	Manual grading of fluorescence intensity	NA
Jeffes EW et al. (2001)	5-ALA20%	14 to 18 h	Not stated	NA	Manual grading of fluorescence intensity	NA
Buinauskaite E et al. (2013)	5-ALA20%	4 h	NA	NA	Manual grading of fluorescence intensity	NA
Sorbellini E et al. (2019)	MAL5%	30 min	NA	NA	Count of fluorescent lesions	NA

^aRepeated applications every 5 min

AK: Actinic keratosis; PDD: Phtodynamic diagnosis.

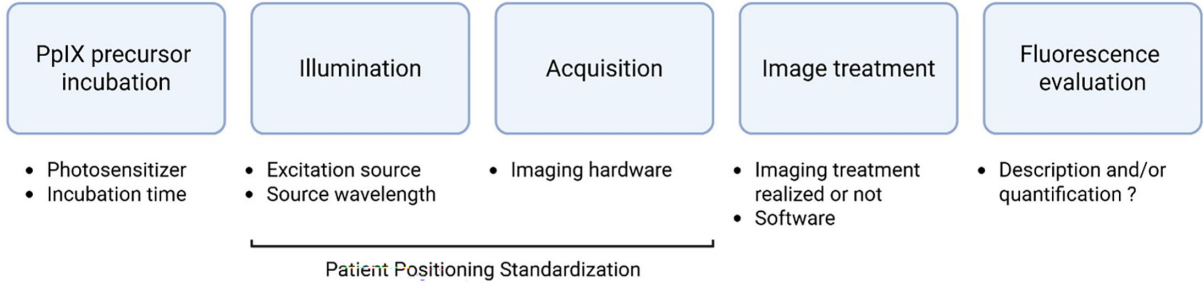


Fig. 2. Data items.

–*Fluorescence acquisition hardware*: Independent cameras were employed in 30% of studies, clinical-grade fluorescence systems in 54%, and smartphone-adapted devices in 5%. No information was reported on the acquisition hardware in the remaining 11% of the studies (Fig. 4).

–*Image treatment and fluorescence assessment*: 54% of the studies reported the use of an image treatment software (e.g. ImageJ) and calibration using a reference standard was often done. Fluorescence intensity could be either precisely quantified (62%) or graded on a scale from high to low or described according to its disposition or extension (22%).

–*Standardization of the patient’s position*: Only 3 articles (8%) reported information about the distance

between the light source and the skin, or the orientation and angle between the skin and light source. (Table II)

DISCUSSION

To our knowledge, this is the first systematic review to describe and summarize the technical landscape of photodynamic diagnosis (PDD) for actinic keratosis (AK) and field cancerization.

Across studies, PDD mostly involved (i) incubation with a protoporphyrin IX precursor and (ii) excitation with violet–blue light (400–410 nm), to induce red fluorescence (600 to 700 nm) detectable by cameras or eyes. Subsequent image processing – to quantify signal intensity or enhance lesion visibility – was often described.

Two PDD implementation strategies dominate. On the one hand, commercial systems integrate dedicated blue-light sources, cameras and post-treatment software, offering reproducibility at a high cost. On the other hand, custom-built or “low-cost” set-ups repurpose and combine readily available components ((e.g.) Wood’s lamp, smartphone), enhancing accessibility but at the expense of standardization.

Standardization is a critical barrier to effective comparability. First fluorescence intensity is highly dependent on precursor type, concentration and application volume, all 3 of which unfortunately vary widely across studies. Then, fluorescence intensity

Table II. Summary of technical parameters in studies on PDD of AK (n=37)

Category	Parameter	Studies n (%)
Photosensitizer	Methyl aminolevulinate (MAL)	20 (54%)*
	Aminolevulinic acid (ALA)	19 (51%)*
	Both MAL and ALA	2 (5%)
Incubation time	3 h	26 (70%)
	Other (20–1080 min)	11 (30%)
Excitation source	Source types	
	Clinical-grade fluorescence system	20 (54%)
	- Dyaderm system	11 (30%)
	- Medeikonos system	7 (19%)
	- FotoFinder system	2 (5%)
	Wood’s lamp	6 (16%)
	UV dermoscope ((e.g.) dermlite DL5)	1 (3%)
	Other blue light ((e.g.) LEDs)	10 (27%)
	Source wavelength	
	Wavelength reported as 400–410 nm	24 (65%)
	365 nm	2 (5%)
	442 nm	1 (3%)
Imaging hardware	Not reported	10 (27%)
	Clinical-grade fluorescence system	20 (54%)
	Separate camera	11 (30%)
	Smartphone-adapted device	2 (5%)
	Not reported	4 (11%)
Image treatment	Image processing software used ((e.g.) ImageJ)	20 (54%)
	None or not specified	17 (46%)
Fluorescence assessment	Quantitative fluorescence measurement	23 (62%)
	Semi-quantitative or descriptive assessment	8 (22%)
	None or not specified	6 (16%)
Patient positioning standardization	Protocol described	3 (8%)
	None or not specified	34 (92%)

Notes: - *Some studies reported more than one photosensitizer, so percentages may exceed 100%.

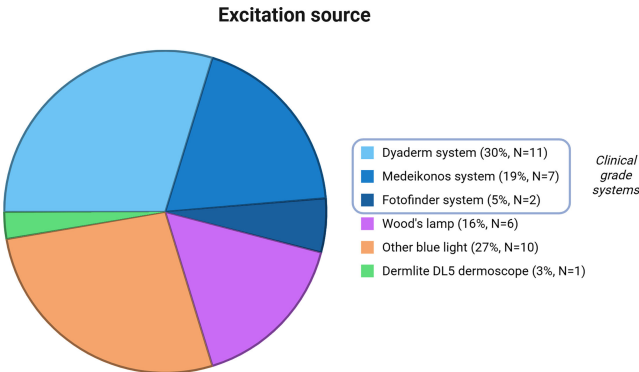


Fig. 3. Excitation source.

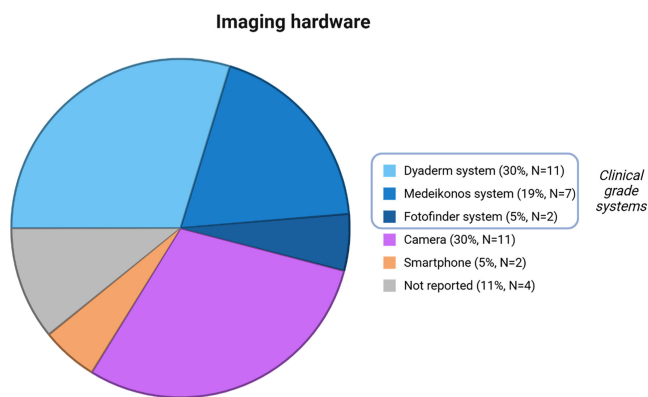


Fig. 4. Imaging hardware.

is subject to excitation specifications (intensity) that are rarely reported in detail. Finally, fluorescence intensity depends on the source-to-skin distance, camera angle, ambient lighting, yet only 3 studies specified a systematic positioning protocol. This heterogeneity limits meta-analysis and hinders the establishment of reference thresholds.

Understanding these methodological variants can help clinicians tailor PDD to their practice. Where longitudinal or inter-patient comparisons are required, strict protocol harmonization including fixed geometry and calibrated light source is critical and essential. Precise reporting of each procedural step would facilitate the development of a global reference method and accelerate multicentre validation.

Finally, large prospective trials are required to assess the diagnostic performance of PDD compared to histopathology and emerging high-resolution imaging modalities such as line-field confocal optical coherence tomography or reflectance confocal microscopy. Whether PDD ultimately occupies a screening, triage or therapy-monitoring niche will depend on such performance assessment. The current diversity of techniques may signal a lack of consensus, but it also underscores the inherent simplicity of PDD: with minimal equipment, clinically useful fluorescence can be obtained. Custom systems offer affordability, whereas integrated platforms provide reproducibility.

This review has several limitations. First, only English-language studies were included, potentially introducing language bias. Second, the specific clinical rationale for employing PDD was not extracted due to substantial variability across studies, limiting insights into the motivation behind methodological choices. Third, publication bias might exist, meaning the techniques most frequently used in clinical practice could differ from those reported in published literature.

An ideal photodiagnosis device should demonstrate high efficacy with a short incubation time, allowing rapid and practical clinical application. It should enable the assessment of large skin areas – such as the entire scalp – in a single acquisition to enhance efficiency

and patient comfort. Ensuring reproducible fluorescence measurements within the same patient over time is critical for reliable longitudinal evaluation. Moreover, a portable system operating independently of ambient lighting conditions would facilitate standardized use across diverse clinical environments and support broader implementation of photodiagnosis techniques in dermatologic practice. The implementation of artificial intelligence to PDD could be highly valuable in terms of fluorescence quantification and discrimination between malignant and benign tissue, independently from user experience.

Other imaging modalities such as LC-OCT could benefit from the combination with PDD, to obtain both anatomical and functional evaluation.

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Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

The authors have no conflicts of interest to declare.

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