MP 2.01.44
Dermatologic Applications of Photodynamic Therapy

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POLICY
Photodynamic therapy may be considered medically necessary as a treatment of:

- Nonhyperkeratotic actinic keratoses of the face and scalp (see policy guidelines).
- Nonhyperkeratotic actinic keratoses of the upper extremities (see policy guidelines).
- Low-risk (e.g., superficial and nodular) basal cell skin cancer only when surgery and radiation are contraindicated.
- Cutaneous squamous cell carcinoma in situ (Bowen disease) only when surgery and radiation are contraindicated.

Photodynamic therapy is considered investigational for other dermatologic applications, including, but not limited to, acne vulgaris, high-risk basal cell carcinomas, hidradenitis suppurativa, and mycoses.

Photodynamic therapy as a technique of skin rejuvenation, hair removal, or other cosmetic indications is considered not medically necessary.

POLICY GUIDELINES
Surgery and radiation are the preferred treatments for low-risk basal cell cancer and Bowen disease (see Rationale section). If photodynamic therapy is selected for these indications because of contraindications to surgery or radiation, patients and physicians need to be aware that it may have a lower cure rate than surgery or radiation.

Photodynamic therapy typically involves 2 office visits: one to apply the topical aminolevulinic acid and a second visit to expose the patient to blue light. The second physician office visit, performed solely to
administer blue light, should not warrant a separate Evaluation and Management CPT code. Photodynamic protocols typically involve 2 treatments spaced a week apart; more than 1 treatment series may be required.

Based on characteristics of patients enrolled in randomized controlled trials, 4 or more lesions per site (face, scalp, or upper extremities) is an appropriate threshold for use of photodynamic therapy for patients with nonhyperkeratotic actinic keratosis.

Coding

See the Codes table for details.

**BACKGROUND**

**Photodynamic Therapy**

PDT refers to light activation of a photosensitizer to generate highly reactive intermediaries, which ultimately cause tissue injury and necrosis. Two common photosensitizing agents are 5-aminolevulinic acid (5-ALA) and its methyl ester, methyl aminolevulinate. When applied topically, these agents pass readily through abnormal keratin overlying the lesion and accumulate preferentially in dysplastic cells. The agents 5-ALA and methyl aminolevulinate are metabolized by underlying cells to photosensitizing concentrations of porphyrins. Subsequent exposure to photoactivation (maximum absorption at 404 to 420 nm and 635 nm) generates reactive oxygen species that are cytotoxic, ultimately destroying the lesion. PDT can cause erythema, burning, and pain. Healing occurs within 10 to 14 days, with generally acceptable cosmetic results. PDT with topical ALA has been investigated primarily as a treatment of actinic keratoses (AKs).

**Regulatory Status**

In 1999, Levulan® Kerastick™, a topical preparation of ALA, in conjunction with illumination with the BLU-U™ Blue Light Photodynamic Therapy Illuminator, was approved by the U.S. Food and Drug Administration (FDA) for the treatment of nonhyperkeratotic AKs of the face and scalp. In 2018, the indication was expanded to include nonhyperkeratotic AKs of the upper extremities. The product is applied in the physician’s office. FDA product code: MVF.

In 2016, the FDA approved Ameluz® (aminolevulinic acid hydrochloride) gel, 10% (BF-200 ALA; Biofrontera AG) in combination with PDT using BF-RhodoLED lamp, to be used for the lesion-directed and field-directed treatment of AKs of mild-to-moderate severity on the face and scalp. The treatment is to be administered by a healthcare provider.

A 5-ALA patch technology is available outside of the US through an agreement between Intendis (now Bayer HealthCare) and Photonamic. The 5-ALA patch is not approved by the FDA.
Another variant of PDT for skin lesions is Metvixia® used with the Aktilite CL128 lamp, each of which received the FDA approval in 2004. Metvixia® (Galderma; Photocure) consists of the topical application of methyl aminolevulinate (in contrast to ALA used in the Kerastick™ procedure), followed by exposure with the Aktilite CL128 lamp, a red light source (in contrast to the blue light source in the Kerastick™ procedure). Broadband light sources (containing the appropriate wavelengths), intense pulsed light (FDA product code: ONF), pulsed dye lasers, and potassium-titanyl-phosphate lasers have also been used. Metvixia® is indicated for the treatment of nonhyperkeratotic AKs of the face and scalp in immunocompetent patients when used with lesion preparation (debridement using a sharp dermal curette) in the physician's office when other therapies are unacceptable or considered medically less appropriate. FDA product codes: GEX and LNK.

**RATIONALE**

The evidence review was created in November 2001 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through November 1, 2019.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. The key literature is described next and focuses on studies evaluating the U.S. Food and Drug Administration (FDA)-approved photosensitizing agents.

**Actinic Keratoses**

**Clinical Context and Test Purpose**

The purpose of photodynamic therapy (PDT) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with nonhyperkeratotic AKs on the face or scalp.

The question addressed in this evidence review is: Does the use of PDT improve the net health outcome for nonhyperkeratotic AKs on the face or scalp.

The following PICOs were used to select literature to inform this review.

**Patients**

The relevant population of interest are individuals with nonhyperkeratotic AKs on the face, scalp, or upper extremities. AKs are rough, scaly, or warty premalignant growths on the sun-exposed skin that are...
very common in older people with fair complexions, with a prevalence of greater than 80% in fair-skinned people older than 60 years of age. In some cases, AKs may progress to squamous cell carcinoma.

Interventions

The therapy being considered is photodynamic therapy.

Patients with nonhyperkeratotic AKs on the face, scalp, or upper extremities are actively managed by dermatologists and oncologists in an outpatient setting.

Comparators

The following therapies are currently being used to treat nonhyperkeratotic AKs on the face, scalp, or upper extremities: pharmacologic therapy, cryotherapy, and laser therapy. Available treatments for AKs can be divided into surgical and nonsurgical methods. Surgical treatments used to treat one or a small number of dispersed individual lesions include excision, curettage (either alone or combined with electrodesiccation), and laser surgery. Nonsurgical treatments include cryotherapy, topical chemotherapy (5-fluorouracil [5-FU] or masoprocol creams), chemexfoliation (chemical peels), and dermabrasion. Topical treatments are generally used in patients with multiple lesions and involve extensive areas of skin. Under some circumstances, combinations of treatments may be used.

Outcomes

The general outcomes of interest are symptoms, change in disease status, QoL, and treatment-related morbidity.

The duration of follow-up is related to the extent of treated disease and is expected to be at least 12 months.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Actinic Keratoses on the Face or Scalp

Systematic Reviews

Patel et al (2014) published a systematic review of RCTs with at least 10 patients that addressed the efficacy of topical PDT compared with an alternative (ie, non-PDT) treatment of AKs. Thirteen studies (total n=641 participants) met the reviewers’ inclusion criteria. Studies compared PDT with cryotherapy (n=6), 5-FU (n=2), imiquimod (n=4), and carbon dioxide laser (n=1). Seven studies used ALA, and the other six used methyl aminolevulinate (MAL) as the PDT sensitizer. Most studies focused on facial or scalp lesions. No study in the review was double-blinded. In 12 of the 13 studies, the primary outcome was a measure related to the clearance rate of lesions. Data from four RCTs comparing PDT with cryotherapy were suitable for meta-analysis. The pooled lesion response rate 3 months after treatment was significantly higher with PDT than with cryotherapy (pooled relative risk [RR], 1.14, 95% confidence interval [CI], 1.11 to 1.18). Due to heterogeneity among the interventions, other data were not pooled.
Randomized Controlled Trials

Pariser et al (2003) conducted a randomized, placebo-controlled trial of 80 patients with AKs. They reported the complete response (CR) rate for the MAL group was 89% and 38% in the placebo group.

Morton et al (2006) published an industry-sponsored, 25-center, randomized, left-right comparison of single PDT and cryotherapy in 119 subjects with AKs on the face or scalp. At a 12-week follow-up, PDT resulted in a significantly higher rate of cured lesions (86.9%) than cryotherapy (76.2%). Lesions with a non-CR retreated after 12 weeks; a total of 108 (14.9%) of 725 lesions received a second PDT session; 191 (26.8%) of 714 lesions received a second cryotherapy treatment. At 24 weeks, groups showed equivalent clearance rates (85.8% vs 82.5%, respectively). Greater skin discomfort was reported with PDT than with cryotherapy. Investigator-rated cosmetic outcomes showed no difference in the percentages of subjects with poor cosmetic outcomes (0.3% vs 0.5%, respectively), with more subjects rated as having excellent outcomes at 24 weeks after PDT (77.2% vs 49.7%, respectively). With PDT, 22.5% had cosmetic ratings of fair or good compared with 49.9% for cryotherapy.

A double-blind RCT conducted in Germany by Hauschild et al (2009) evaluated PDT with 5-aminolevulinic acid (5-ALA) using a self-adhesive patch. Eligibility criteria included white patients, age 18 years and older, with skin type I to IV (pale to olive complexion), and AKs on the head of mild or moderate grade, as defined by Cockerell (maximum diameter, 1.8 cm; intralessional distance, at least 1 cm). Patients were randomized to 5-ALA patches at 8 mg or identical placebo patches. Patches were square, measuring 4 cm², and patients received three to eight of them, depending on the number of study lesions. The primary efficacy outcome was the complete clinical clearance rate 12 weeks after PDT. A total of 99 of 103 randomized patients were included in the primary efficacy analysis. Complete clinical clearance rate on a per-patient basis (all lesions cleared) was 62% (41/66) in the 5-ALA patch group and 6% (2/33) in the placebo patch group; there was a statistically significant difference favoring PDT.

Szeimies et al (2010) reported on a phase 3 clinical trial using a stable 5-aminolaevulinic acid nanoemulsion formulation (BF-200 ALA) developed for PDT for AKs. The multicenter, double-blind, interindivudual 2 armed-trial randomized 122 patients to BF-200 ALA or placebo. The patients had four to eight mild-to-moderate AKs lesions on the face and/or bald scalp. BF-200 ALA was used in combination with 1 of 2 different light sources. The efficacy of BF-200 ALA after the first PDT treatment was evaluated at 12 weeks. For patients who were not completely cleared of AKs received a second PDT treatment, with the final evaluation 12 weeks later for all participants. The results showed PDT with BF-200 ALA was superior to PDT with a placebo in respect to patient complete clearance rate (per-protocol group, 64% vs 11%; p<0.001) and lesion complete clearance rate (per-protocol group, 81% vs 22%) after the last PDT treatment. Statistically significant differences in the patient and lesion complete clearance rates and adverse event profiles were observed for the 2 light sources (Aktlite CL128 and PhotoDyn 750) at both time points of the assessment. The patient and lesion complete clearance rates after illumination with the AktliteCL128 were 96% and 99%, respectively. No adverse events (discomfort, pain) were mentioned by patients related to the application of the gel prior to PDT treatment. Burning and itching were reported during or after the red light illumination. Moreover, 100% of patients treated using Aktlite CL128 had burning after the second PDT session. Of the patients treated using PhotoDyn 750, 60% reported pain during or after PDT. A limitation of the study was its lack of follow-up for patients beyond study protocols.

Szeimies et al (2010) in Germany reported 12-month follow-up data from a study comparing PDT using a self-adhesive patch with cryotherapy. The study had the same eligibility criteria and primary outcome as the Hauschild et al (2009) study (previously described). A total of 148 patients were randomized to a 5-ALA patch group, 49 to a placebo group, and 149 to a cryotherapy group. The study used a test of
noninferiority of PDT vs cryosurgery. Fourteen patients who dropped out were excluded from the analysis comparing PDT with cryotherapy. The rate of complete clearance of all lesions was 67% (86/129) in the 5-ALA group, 52% (66/126) in the cryosurgery group, and 12% (5/43) in the placebo group. The clearance rate was significantly higher in the 5-ALA patch group than in either comparator group. Results were similar in the analysis of clearance rates on a per lesion basis. The 360 patients with at least 1 lesion cleared at 12 weeks were followed for an additional 9 months; 316 patients completed the final visit 1 year after treatment. Overall clearance rate on a lesion basis was still statistically higher in the 5-ALA patch group than in the placebo (in both studies) and the cryosurgery (in the second study) groups. Moreover, 32% of patients in the 5-ALA group from the first study and 50% of patients in the 5-ALA group from the second study were still completely free from lesions by the end of the trial. The corresponding rate in the cryosurgery group was 37%. In the safety analysis, there were high rates of local reaction to patch application and cryotherapy at the time of treatment; however, no serious adverse events due to study intervention were documented.

A randomized pilot study by Serra-Guillen et al (2012) Spain compared PDT using MAL alone, imiquimod alone, and the combination of the 2 treatments.7 Patients with nonhyperkeratotic AKs on the face and/or scalp were randomized to 1 of 3 groups: (1) 1 session of PDT with MAL (n=40); (2) self-administered imiquimod 5% cream for 4 weeks (n=33); or (3) treatment as with group 1 followed by 4 weeks of imiquimod cream (n=32). Follow-up occurred one month after PDT (group 1) or one month after the end of treatment with imiquimod (groups 2 and 3). The primary outcome measure (complete clinical response) was defined as the total absence of AKs by visual evaluation and palpation. Complete clinical response was achieved by 4 (10%) of patients in group 1, 9 (27%) of patients in group 2, and 12 (37.5%) of patients in group 3. There was a statistically significantly higher rate of CR in the PDT plus imiquimod group compared with PDT only (p=0.004). A study limitation was that the PDT-only group had a shorter follow-up, which could at least partially explain the lower rate of CR.

Dirschka et al (2012) reported on an industry-sponsored randomized, multicenter, observer-blind, placebo-controlled, interindividual trial comparing BF-200 ALA for the treatment of AKs with MAL cream and placebo.8 Six hundred patients with 4 to 8 mild-to-moderate AKs lesions on the face and/or bald scalp were enrolled in 26 study centers. Five hundred forty-nine patients completed the study. Early dropouts were reported, including 15 patients for unexplained reasons, 4 patients with adverse events associated with treatment, and 2 patients with protocol violations. The trial results showed PDT with BF-200 ALA was superior to placebo PDT with respect to patient complete clearance rate (78.2% vs 17.1%; p<0.001) and lesion complete clearance rate (90.4% vs 37.1%) at 3 months after the last PDT, respectively. Superiority was demonstrated over the MAL cream for the primary endpoint of patient complete clearance (78.2% vs 64.2%; p<0.05). Significant differences in the patient and lesion complete clearance rates and severities of treatment-related adverse events were observed for the narrow- and broad-spectrum light sources. Patient clearance rates and lesion clearance rates were higher compared with MAL. Table 1 provides the data on the light source affecting the clearance rates.

Table 1. Summary of Key RCT Results for Light Source Effects on Clearance Rates

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients/Lesions</th>
<th>Patient Total Clearance Rate</th>
<th>Lesion Total Clearance Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Narrow-Light Spectrum, %</td>
<td>Broad-Light Spectrum, %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Narrow-Light Spectrum, %</td>
<td>Broad-Light Spectrum, %</td>
</tr>
<tr>
<td>Dirschka et al (2012)</td>
<td>248/1504</td>
<td>54.0</td>
<td>46.5</td>
</tr>
<tr>
<td>One BF-200 ALA treatment</td>
<td>248/1504</td>
<td>54.0</td>
<td>46.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>77.1</td>
<td>69.7</td>
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</table>
Drischka et al (2013) reported on the follow-up phase of patients from 2, phase 3 studies that compared BF-200 ALA (n=329) with placebo (n=117) or MAL (n=247) for the treatment of AKs. No safety concerns were reported. Recurrence rates were similar for BF-200 ALA and MAL. The percentage of patients who achieved complete clearance with PDT and remained completely clear for at least 12 months after PDT were 47% for BF-200 ALA and 36% for MAL treatment. The authors reported that the follow-up phase data confirmed the efficacy and safety of PDT with BF-200 ALA. No p-values or CIs were reported.

In 2014, 3 RCTs compared different light sources for PDT in the treatment of AKs. One trial used 5-ALA, the second trial used MAL cream, and the third reported on the use of MAL and BF-200 ALA using daylight-mediated PDT. There was no clear evidence of the superiority of the different light sources over another. Some of the alternative approaches (eg, daylight PDT) have not been cleared by the FDA.

Zane et al (2014) published the results of an RCT on the treatment of multiple AKs of the face and scalp. The trial compared MAL-PDT with diclofenac 3% plus hyaluronic acid gel (DHA). Two hundred patients were enrolled. At 3 months, the complete remission rate was 85.9% for patients using MAL-PDT and 51.8% for patients using DHA (p<0.001). Incomplete responses to MAL-PDT were followed by a second treatment. At 12 months, the complete remission rate was 37% for patients treated with MAL-PDT and 7% for patients treated with DHA. Based on these results, the authors determined MAL-PDT was “superior in comparison with DHA for the treatment of actinic keratosis.” Potential weaknesses in the DHA arm were that patients self-administered the DHA gel and had a longer treatment cycle (90 days) than the MAL-PDT arm.

Reinhold et al (2016) published results from a double-blind RTC comparing BF-200 ALA with placebo for the field-directed treatment of mild-to-moderate AKs with PDT using the BF-Rhodo LED lamp. After a maximum of 2 PDT treatments the results, measured 12 weeks after the last PDT, showed a patient complete clearance rate of 91% using BF-200 ALA vs 22% using placebo (p<0.001), and a lesion complete clearance rate of 94.3% using BF-200 ALA vs 32.9% using placebo (p<0.001). There were treatment adverse events in 100% of the BF-200 ALA group and in 69% of the placebo group. The adverse events were application-site events and included site pain, erythema, pruritus, scab, exfoliation, edema, and vesicles. Local skin reactions were of mild-to-moderate intensity. Application-site pain was the most common individual adverse event in both groups (96.4% for BF-200 ALA vs 50.0% for placebo) and was rated as severe by 49% of the BF-200 ALA group and 3% of the patients treated with placebo. One of 32 patients in the placebo group and no patients in the BF-200 ALA group displayed a new lesion after PDT. Trialists indicated that this result may be the preventive effect of field-directed AKs treatment.

Yazdanyar et al (2017) published results from a clinical trial on pain during topical PDT, which compared MAL (Metvix) with 5-ALA (Ameluz). Patients with mild-to-moderate AKs on forehead and scalp were treated with MAL-PDT and ALA-PDT on two similar areas of forehead and scalp. Fourteen patients completed the MAL-PDT and ALA-PDT treatments. The pattern of pain intensity was similar for both groups. Both treatments were painful, which gradually intensified during the first minute of treatment, reaching a maximum within the first five minutes. The pain eased immediately after the PDT treatment.
The authors reported no significant difference in pain intensity between MAL-PDT and ALA-PDT, during the treatment (p=1.0) and 30 minutes after the treatment (p=0.19). Pain was the only outcome reported in this trial. Trial limitations included the lack of blinding by the nurse who administered the treatment and patient perception (because both sides were painful, the patients could not distinguish between small differences in pain intensity).

Section Summary: AKs on the Face or Scalp

Evidence from multiple RCTs has suggested that PDT improves the net health outcome in patients with nonhyperkeratotic AKs of the face or scalp compared with placebo or other active interventions. Study limitations for the trials comparing MAL with BF-200 ALA included results using different light sources and the use of non-FDA approved light sources, self-reported pain assessments, and self-administered topical treatment. There is insufficient evidence to suggest that any PDT protocol is superior to another.

Actinic Keratoses on the Upper Extremities

Randomized Controlled Trials

Three placebo-controlled RCTs used ALA and PDT with blue light (Tables 2 and 3). The largest and most recent of these, Jiang et al (2019), was the basis for the FDA approval of Levulan Kerastick for the treatment of AKs on the upper extremities. Two of these had a similar design: individual patients were randomized to active treatment or placebo, patients were re-treated at 8 weeks if any AKs remained, and outcomes were reported at 8 and 12 weeks. In both, significantly more patients had a complete clearance of all lesions after 12 weeks. The most common adverse events were stinging/burning during light treatment and erythema after light treatment, no subjects withdrew from treatment due to adverse events in Jiang et al (2019), and 2 requested early withdrawal in Schmieder et al (2012). Schmieder et al (2012) additionally randomized patients to occlusion or no occlusion on alternate extremities and found better results with occlusion. Taub et al (2011) was a small (n=15), 4-week, intra-individual study in which patients were randomized to receive active treatment or placebo on alternate arms. At four weeks, no patients experienced complete clearance, but the mean lesion count was significantly lower in the treatment group compared to the placebo.

Two other small RCTs compared ALA/PDT using red light to imiquimod or 5-FU and found similar efficacy between the active treatment groups after six months of follow-up (Tables 2 and 3).

Study limitations are summarized in Tables 3 and 4.

Table 2. Characteristics of RCTs of PDT for AKs on the Upper Extremities

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Design</th>
<th>Participants</th>
<th>Interventions</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Active</td>
<td>Comparator</td>
</tr>
<tr>
<td>Jiang et al</td>
<td>U.S.</td>
<td>13</td>
<td>2014-2015</td>
<td>Parallel</td>
<td>269 adults 18 or older with 4 or 15 Grade 1 or 2 AKs on one upper extremity</td>
<td>20% ALA-blue light PDT N=135</td>
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<tr>
<td>(2019)\textsuperscript{16} NCT02137785</td>
<td></td>
<td></td>
<td></td>
<td>groups</td>
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<tr>
<td>Schmieder et</td>
<td>U.S.</td>
<td>3</td>
<td>2012</td>
<td>Parallel</td>
<td>70 adults 18 or older with at least 4 Grade 1 or 2</td>
<td>20% ALA-blue light</td>
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<td>al (2012)\textsuperscript{17} NCT01458587</td>
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<td>groups</td>
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</table>
**Table 3. Results of RCTs of PDT for AKs on the Upper Extremities**

<table>
<thead>
<tr>
<th>Study</th>
<th>Complete Clearance</th>
<th>Lesion Reduction</th>
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</thead>
</table>
ALA-PDT               | 8 weeks: 35/135 (25.9%)  
12 weeks: 42/135 (31.1%) |                  |
| Schmieder et al (2012)  
ALA-PDT               | 8 weeks: 8/35 (22.9%)  
12 weeks: 12/35 (34.3%) |                  |
| Schmieder et al (2012)  
VEH-PDT               | 8 weeks: 0/35 (0%)  
12 weeks: 1/35 (2.9%) |                  |
| Taub et al (2011)    | 0.002 at 12 weeks; 8 weeks NR | Mean (SD) lesion count |

RCT: randomized controlled trial; PDT: photodynamic therapy; AKs: actinic keratoses; ALA: aminolevulinic acid; VEH: vehicle (placebo); NR: not reported; 5-FU: 5-fluorouracil.
### Dermatologic Applications of Photodynamic Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
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<tr>
<td>Taub et al (2011)</td>
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<td>Patient</td>
<td></td>
<td>1. complete clearance not reported</td>
<td>1. 4 weeks</td>
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<td>1. complete clearance not reported</td>
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### Table 4. Relevance Limitations

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<tr>
<td>Jiang et al (2019)</td>
<td>NCT02137785</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmieder et al (2012)</td>
<td>NCT01458587</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taub et al (2011)</td>
<td></td>
<td>Patient</td>
<td></td>
<td>1. complete clearance not reported</td>
<td>1. 4 weeks</td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

### ALA-PDT

<table>
<thead>
<tr>
<th>ALA-PDT</th>
<th>Reduction at 4 weeks</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEH-PDT</td>
<td>58.4% (22.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sotiriou et al (2009)

<table>
<thead>
<tr>
<th>ALA-PDT</th>
<th>4 weeks: 87/124 (70.16%) 6 months: 81/124 (65.32%); 95% CI, 56.9 to 73.7%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imiquimod</td>
<td>4 weeks: 21/115 (18.26%) 6 months: 64/115 (55.65%); 95% CI, 46.6 to 64.7%</td>
</tr>
</tbody>
</table>

p-value  

<0.05 at 4 weeks

>0.05 at 6 months


<table>
<thead>
<tr>
<th>Mean reduction in lesion area at 6 months:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALA-PDT</td>
</tr>
<tr>
<td>73% (95% CI 61%-84%).</td>
</tr>
<tr>
<td>5-FU</td>
</tr>
<tr>
<td>70% (95% CI 61% to 80%)</td>
</tr>
<tr>
<td>Difference</td>
</tr>
<tr>
<td>2% (95% CI, –10% to 14%; P = .721)</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; PDT: photodynamic therapy; AKs: actinic keratoses; ALA: aminolevulinic acid; CI: confidence interval; VEH: vehicle (placebo); NR: not reported; SD: standard deviation; 5-FU:5-fluourouracil.
**Dermatologic Applications of Photodynamic Therapy**

\[d\] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

\[e\] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

### Table 5. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocationa</th>
<th>Blindingb</th>
<th>Selective Reportingc</th>
<th>Data Completenessd</th>
<th>Powere</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiang et al (2019)[^{16}] NCT02137785</td>
<td>3. allocation concealment method not reported</td>
<td>1. Outcome assessors, but not patients, were blinded</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmieder et al (2012)[^{17}] NCT01458587</td>
<td>3. allocation concealment method not reported</td>
<td>1. Outcome assessors, but not patients, were blinded</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taub et al (2011)[^{18}]</td>
<td>3. allocation concealment method not reported</td>
<td>1. Outcome assessors, but not patients, were blinded</td>
<td></td>
<td>1. small sample size (N=15), no power calculation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotiriou et al (2009)[^{19}]</td>
<td>3. allocation concealment method not reported</td>
<td>1. Not blinded</td>
<td></td>
<td>1. small sample size (N=30), no power calculation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kurwa et al (1999)[^{20}]</td>
<td>3. allocation concealment method not reported</td>
<td>1. Not blinded</td>
<td></td>
<td>1. small sample size (N=17), no power calculation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.


\[^{b}\] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.


\[^{d}\] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing
data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: AKs on the Upper Extremities

In two placebo-controlled RCTs, significantly more patients had a complete clearance of AKs with ALA/PDT with blue light compared to placebo at 12 weeks, and a third found a significantly greater reduction in mean lesion count at 4 weeks. Two small RCTs compared ALA/PDT using red light to imiquimod or 5-FU and found similar efficacy between the active treatment groups after six months of follow-up.

Basal Cell Carcinoma

Clinical Context and Test Purpose

The purpose of PDT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with low-risk BCC.

The question addressed in this evidence review is: Does the use of PDT improve the net health outcome for low-risk BCC?

The following PICOs were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with low-risk BCC. Nonmelanoma skin cancers are the most common malignancies in the white population. Most often found in light-skinned individuals, BCC is the most common of the cutaneous malignancies. Although BCC tumors rarely metastasize, they can be locally invasive if left untreated, leading to significant local destruction and disfigurement. The most prevalent forms of BCC are nodular BCC and superficial BCC.

Interventions

The therapy being considered is PDT.

Patients with low-risk BCC are actively managed by dermatologists and oncologists in an outpatient setting.

Comparators

The following therapies are currently being used to treat BCC: pharmacologic therapy, cryotherapy, surgery, and radiotherapy. Excision surgery is the preferred treatment for smaller nonmelanoma skin lesions and those not in problematic areas, such as the face and digits. Other established treatments include topical 5-FU, imiquimod, and cryotherapy.

Outcomes

The general outcomes of interest are symptoms, change in disease status, QOL, and treatment-related morbidity.

Duration of follow-up is dependent on the extent of lesions and evaluation at 1, 3, and 12 months would be appropriate.
Study Selection Criteria
Methodologically credible studies were selected using the principles outlined for indication 1.

Systematic Reviews
Wang et al (2017) published a systematic review of RCTs on PDT for treating BCC, both superficial and nodular types. To be selected, studies had to include adults with one or more primary BCCs, randomize participants to PDT, placebo, or another treatment, and report the complete clearance rate, recurrence rate, cosmetic outcomes, and/or adverse events rate. Eight RCTs (total n=1583 patients), published between 2001 and 2013, met inclusion criteria. Three trials included patients with superficial BCC; three included patients with nodular BCC and one trial included patients with both types of low-risk BCC. Four trials compared PDT with surgery, two compared PDT with cryotherapy, one compared PDT with pharmacologic treatment, and one was placebo-controlled.

In a meta-analysis of 7 studies, the estimated probability of complete clearance after treatment was similar in the PDT and the non-PDT groups (RR=0.97; 95% CI, 0.88 to 1.06). In subgroup analyses by treatment type, PDT was associated with a significantly higher clearance rate only compared with the placebo. Surgery was associated with a significantly lower rate of recurrence compared with PDT, and there was no significant difference in recurrence rates when PDT was compared with cryotherapy and pharmacologic therapy. In meta-analyses of cosmetic outcomes at 1 year, there was a significantly higher probability of a good-to-excellent outcome with PDT than with surgery (RR=1.87; 95% CI, 1.54 to 2.26) or cryotherapy (RR=1.51; 95% CI, 1.30 to 1.76).

A meta-analysis by Zou et al (2016) identified 5 RCTs comparing PDT with surgical excision in patients who had nodular BCC and at least 3 months of follow-up. The rate of CR was significantly lower in the PDT group than in the surgical excision group at 1 year (RR=0.89; 95% CI, 0.80 to 0.99) and at 3 years (RR=0.73; 95% CI, 0.63 to 0.85); there were no significant differences in CR at 2, 4, or 5 years. The rate of recurrence was significantly higher in the PDT group than in the surgical excision group at all time points.

A Cochrane review by Bath-Hextall et al (2007) evaluated surgical, destructive (including PDT), and chemical interventions for BCC. Reviewers concluded that surgery and radiotherapy appeared to be the most effective treatments, with the best results obtained using surgery. In addition, they stated that cosmetic outcomes appear to be good with PDT, but additional data with long-term follow-up are needed. Cochrane reviewers did not distinguish among BCC subtypes.

Randomized Controlled Trials
A noninferiority RCT by Roozeboom et al (2016) compared MAL-PDT with imiquimod cream and with fluorouracil cream in patients with superficial BCC. A total of 601 patients were randomized, 202 to MAL-PDT, 198 to imiquimod, and 201 to fluorouracil. A total of 490 (82%) patients completed the 1-year follow-up and 417 (69%) completed the 3-year follow-up. Median follow-up was 35 months. The estimated tumor-free survival rates at 3 years were 58% (95% CI, 47.8% to 66.9%) in the PDT group, 79.7% (95% CI, 71.6% to 85.7%) in the imiquimod group, and 68.2% (95% CI, 58.1% to 76.3%) in the fluorouracil group. Results of the noninferiority analysis suggested that imiquimod was superior to MAL-PDT and imiquimod was noninferior to MAL-PDT.

An industry-sponsored multicenter RCT was published by Szeimies et al (2008). This trial compared MAL-PDT with surgery for small (8-20 mm) superficial BCC in 196 patients. At 3 months posttreatment, 92% of lesions treated with MAL-PDT showed a clinical response, compared with 99% of lesions treated with surgery (per-protocol analysis). At a 12-month follow-up, no lesion recurrence was reported in the surgery group, while the recurrence rate was 9% in the MAL-PDT group. Approximately 10% of patients...
discontinued MAL-PDT due to an incomplete response or adverse event compared with 5% of patients in the surgery group. Cosmetic outcomes were rated by the investigators as good-to-excellent in 94% of lesions treated with MAL-PDT and 60% after surgery.

Rhodes et al (2007) published a 5-year follow-up to an industry-sponsored multicenter randomized trial comparing MAL-PDT with surgery for nodular BCC.26,27 A total of 101 adults with previously untreated nodular BCC were randomized to MAL therapy or surgery. At 3 months, CR rates did not differ between groups; however, at 12 months, the CR rate had fallen from 91% to 83% in the MAL-PDT group, and from 98% to 96% in the surgery group. Of 97 patients in the per-protocol population, 66 (68%) were available for a 5-year follow-up; 16 (32%) discontinued in the MAL-PDT group due to treatment failure or adverse events vs 6 (13%) in the surgery group. A time-to-event analysis of lesion response estimated a sustained lesion response rate of 76% for MAL-PDT and 96% for excision surgery. Cosmetic outcomes were rated as good-to-excellent in 87% of the MAL-PDT patients and in 54% of the surgery patients.

Section Summary: BCC

Systematic reviews of RCTs have found that PDT may not be as effective as surgery for superficial and nodular BCC. In the small number of trials available, PDT was more effective than a placebo. The available evidence from RCTs has suggested that PDT has better cosmetic outcomes than surgery.

Squamous Cell Carcinoma

Clinical Context and Test Purpose

The purpose of PDT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with squamous cell carcinoma in situ (Bowen disease).

The question addressed in this evidence review is: Does the use of PDT improve the net health outcome for squamous cell carcinoma in situ (Bowen disease)?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with squamous cell carcinoma in situ. Bowen disease is a squamous cell carcinoma in situ with the potential for significant lateral spread. Metastases are rare, with less than 5% of cases advancing to invasive squamous cell carcinoma. Lesions may appear on the sun-exposed or covered skin.

Interventions
The therapy being considered is PDT.

 Patients with squamous cell carcinoma in situ are actively managed by dermatologists and oncologists in an outpatient setting.

Comparators
The following therapies are currently being used to treat n squamous cell carcinoma in situ: pharmacologic therapy, cryotherapy, surgery, and radiotherapy.

Outcomes
The general outcomes of interest are symptoms, change in disease status, QOL, and treatment-related morbidity.
Duration of follow-up is dependent on the extent of lesions and evaluation at 1, 3, and 12 months would be appropriate.

Study Selection Criteria

Methodologically credible studies were selected using the principles outlined for indication 1.

Systematic Reviews

Bath-Hextall et al (2013) published a Cochrane review of interventions for cutaneous Bowen disease.28 Reviewers identified seven RCTs evaluating PDT: four compared two PDT protocols, one compared PDT with cryotherapy, one compared PDT with topical 5-FU, and one compared PDT with both PDT and 5-FU. Reviewers did not pool study results.

Randomized Controlled Trials

The largest study (n=225 patients) was a 3-arm trial published by Morton et al (2006).29 This multicenter trial was conducted in 11 European countries. A total of 225 patients were randomized to MAL-PDT, cryotherapy, or 5-FU for treatment of Bowen disease. Unblinded assessment of lesion clearance found PDT to be noninferior to cryotherapy and 5-FU (93% vs 86% vs 83%, respectively) at 3 months and superior to cryotherapy and 5-FU (80% vs 67% vs 69%, respectively) at 12 months. Cosmetic outcomes at 3 months were rated higher for PDT than for standard nonsurgical treatments by both investigators and blinded evaluators, with investigators rating cosmetic outcomes as good or excellent in 94% of patients treated with MAL-PDT, 66% of patients treated with cryotherapy, and 76% of those treated with 5-FU.

Another representative trial comparing PDT with another intervention in patients with Bowen disease was published by Salim et al (2003).30 Forty patients were randomized to topical 5-FU or MAL therapy. Twenty-nine (88%) of 33 lesions in the PDT group cleared completely compared with 22 (67%) of 33 lesions in the 5-FU group. In the 5-FU group, severe eczematous reactions developed around seven lesions, ulceration of three, and erosions of two. No such reactions were noted in the PDT group.

Section Summary: Squamous Cell Carcinoma In Situ (Bowen Disease)

RCTs have found that PDT has similar or greater efficacy than cryotherapy and 5-FU for patients with Bowen disease. Additionally, adverse effects and cosmetic outcomes appeared to be better after PDT. There is a lack of RCTs comparing PDT with surgery or radiotherapy in patients with Bowen disease; as a result, conclusions cannot be drawn about PDT compared with these other treatments.

Nonmetastatic Invasive Squamous Cell Carcinoma

Clinical Context and Test Purpose

The purpose of PDT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with nonmetastatic invasive squamous cell carcinoma.

The question addressed in this evidence review is: Does the use of PDT improve the net health outcome for nonmetastatic invasive squamous cell carcinoma?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with nonmetastatic invasive squamous cell carcinoma.

Interventions
The therapy being considered is PDT.

Comparators

The following therapies are currently being used to treat nonmetastatic invasive squamous cell carcinoma: cryotherapy, surgery, and radiotherapy.

Outcomes

The general outcomes of interest are overall survival, symptoms, change in disease status, QOL, surgery, and radiotherapy.

Timing

Though not completely standardized, follow-up for nonmetastatic invasive squamous cell carcinoma symptoms would typically occur in the months to years after starting treatment.

Setting

Patients with nonmetastatic invasive squamous cell carcinoma are actively managed by dermatologists and oncologists in an outpatient setting.

Study Selection Criteria

Methodologically credible studies were selected using the principles outlined for indication 1.

Systematic Reviews

Lansbury et al (2013) published a systematic review of observational studies evaluating interventions for nonmetastatic cutaneous squamous cell carcinoma. Reviewers identified 14 prospective studies evaluating PDT. Sample sizes ranged from 4 to 71 patients, with only 3 studies including more than 25 patients. The 14 studies evaluated various PDT protocols. Only one was comparative, and it assessed two PDT regimens. In a meta-analysis, a mean of 72% of lesions had a CR to treatment (95% CI, 61.5% to 81.4%; I²=71%). Eight studies addressed recurrence rates in patients who were initial responders. In a meta-analysis, the pooled odds of recurrence were 26.4% (95% CI, 12.3% to 43.7%; I²=72%).

Section Summary: Nonmetastatic Invasive Squamous Cell Carcinoma

No RCTs evaluating PDT for the treatment of nonmetastatic invasive squamous cell carcinoma were found. There are a number of small, uncontrolled studies, and they represent insufficient evidence on which to draw conclusions about the efficacy and safety of PDT for patients with this condition.

Acne

Clinical Context and Test Purpose

The purpose of PDT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with acne.

The question addressed in this evidence review is: Does the use of PDT improve the net health outcome for acne?

The following PICOs were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with acne.

Patients with acne are actively managed by dermatologists and primary care providers in an outpatient setting.
Interventions
The therapy being considered is PDT.

Comparators
The following therapies are currently being used to treat PDT: pharmacologic therapy and laser or light therapy.

Outcomes
The general outcomes of interest are symptoms, change in disease status, QOL, and treatment-related morbidity.

The duration of follow-up would be based on the extent of lesions and 4, 8, and 12 weeks would be appropriate.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined for indication 1.

Systematic Reviews
A Cochrane review by Barbaric et al (2016), addressed a variety of light therapies for acne, including PDT. For studies on MAL-PDT, only data on the investigator-assessed change in lesion counts were suitable for pooling. A meta-analysis of 3 studies on MAL-PDT did not find a significant difference from placebo on investigator-assessed change in inflamed lesion counts (mean difference, -2.85; 95% CI, -7.51 to 1.81) or change in noninflamed lesion counts (mean difference = -2.01; 95% CI, -7.07 to 3.05). Reviewers concluded there is a lack of high-quality evidence on light therapies for treating acne and a low certainty in the usefulness of PDT.

Randomized Controlled Trials
Tables 6 and 7 summarize the characteristics and results of relevant RCTs.

Table 6. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Participants</th>
<th>Interventions</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicklas et al (2018)</td>
<td>Chile</td>
<td>1</td>
<td>46 patients with moderate inflammatory facial acne</td>
<td>ALA-PDT</td>
<td>Doxycycline plus adapalene gel</td>
</tr>
<tr>
<td>Xu et al (2017)</td>
<td>China</td>
<td>1</td>
<td>95 patients with moderate-to-severe facial acne</td>
<td>Minocycline hydrochloride capsule plus PDT</td>
<td>Minocycline hydrochloride capsule without PDT</td>
</tr>
<tr>
<td>Orringer et al (2010)</td>
<td>U.S.</td>
<td>1</td>
<td>44 patients with facial acne, split-faced</td>
<td>ALA-PDT</td>
<td>No treatment</td>
</tr>
</tbody>
</table>

ALA: aminolevulinic acid; MAL-PDT: methyl aminolevulinate; PDT: photodynamic therapy; RCT: randomized controlled trial.

Table 7. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean Reduction in Facial</th>
<th>Adverse Events (%)</th>
</tr>
</thead>
</table>

Original Policy Date: November 2001
### Inflammatory Lesion Count

<table>
<thead>
<tr>
<th>Study</th>
<th>Population(^a)</th>
<th>Intervention(^b)</th>
<th>Comparator(^c)</th>
<th>Outcomes(^d)</th>
<th>Follow-Up(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicklas et al (2018)(^33)</td>
<td></td>
<td>ALA-PDT</td>
<td>-12.0 (median)</td>
<td>P values reported: p = 0.038</td>
<td></td>
</tr>
<tr>
<td>Xu et al (2017)(^34)</td>
<td></td>
<td>Doxycycline plus adapalene gel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xu et al (2017)(^34)</td>
<td></td>
<td>Minocycline hydrochloride capsule plus PDT</td>
<td>-74.4%</td>
<td>Pain (16.7) Burns sensation (14.6) Dizziness (6.3) Headache (4.2) Erythema (8.3) Hyperpigmentation (2.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minocycline hydrochloride capsule without PDT</td>
<td>-53.3%</td>
<td>Dizziness (8.5) Headache (6.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pariser et al (2016)(^35)</td>
<td></td>
<td>MAL-PDT</td>
<td>-15.6</td>
<td>Pain (17)</td>
<td></td>
</tr>
<tr>
<td>Orringer et al (2010)(^36)</td>
<td></td>
<td>Placebo</td>
<td>-7.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orringer et al (2010)(^36)</td>
<td></td>
<td>MAL-PDT</td>
<td>-5.9</td>
<td>Mild peeling (4.5) Hyperpigmentation (4.5) A small blister (2.3)</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td></td>
<td></td>
<td>-2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALA: aminolevulinic acid; MAL-PDT: methyl aminolevulinate; PDT: photodynamic therapy; RCT: randomized controlled trial.

The purpose of limitations tables (see Tables 8 and 9) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

### Table 8. Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Population(^a)</th>
<th>Intervention(^b)</th>
<th>Comparator(^c)</th>
<th>Outcomes(^d)</th>
<th>Follow-Up(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicklas et al (2018)(^33)</td>
<td></td>
<td>4. Small sample size</td>
<td></td>
<td>1. Short follow-up</td>
<td></td>
</tr>
<tr>
<td>Pariser et al (2016)(^35)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orringer et al (2010)(^36)</td>
<td></td>
<td>4. Small sample size</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

\(^a\) Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.


### Table 9. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation(\text{a})</th>
<th>Blinding(\text{b})</th>
<th>Selective Reporting(\text{c})</th>
<th>Data Completeness(\text{d})</th>
<th>Power(\text{e})</th>
<th>Statistical(\text{f})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicklas et al (2018)(33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xu et al (2017)(34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pariser et al (2016)(35)</td>
<td></td>
<td></td>
<td></td>
<td>1. 16% of participants did not complete trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orringer et al (2010)(36)</td>
<td></td>
<td></td>
<td></td>
<td>1. 34% of participants did not complete trial</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.


Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nicklas et al (2018) conducted an RCT involving 46 patients (age range, 18-30 years; 26 male, 20 female) with moderate inflammatory facial acne.\(33\) In the trial, 23 patients received 2 sessions of PDT plus topical aminolevulinic acid, while the other 23 patients received treatments of doxycycline plus adapalene gel. Two blinded dermatologists evaluated all patients at baseline and at 6 and 12 weeks after the start of treatment to count the inflammatory and noninflammatory facial lesions. The PDT group had a significantly higher median percent reduction in noninflammatory lesion count \((p=0.013)\) and total lesions \((p=0.038)\) at 6 weeks. Similar results were found at 12 weeks \((p=0.020)\) for noninflammatory lesions; \(p=0.026\) for total lesions). No severe side effects were observed for either therapy. Trial limitations included small sample size and a short follow-up.
Xu et al (2017) conducted an RCT involving 95 patients (age range, 15-35 years; 41 male, 54 female) to compare the efficacy of minocycline plus PDT with minocycline alone in treating moderate-to-severe acne. In the trial, all patients took a daily minocycline hydrochloride capsule for 4 weeks, and 48 patients also received PDT once a week for 4 weeks. Both groups were evaluated before the study and at two, four, six, and eight weeks after the first treatment. The PDT group reported a greater mean percentage reduction in lesion counts from baseline than the minocycline alone group (-74.4% vs -53.3%; p<0.001) as well as a greater reduction in noninflammatory lesions (-61.7% vs -42.4%; p<0.05). Adverse events were mild and manageable. Limitations included a short follow-up and the lack of broad consensus on quantitative evaluation of acne severity.

Pariser et al (2016) published a multicenter double-blind placebo-controlled, randomized trial evaluating MAL-PDT for severe facial acne. A total of 153 patients were randomized and included in the intention-to-treat analysis. All patients received 4 treatments, 2 weeks apart and were evaluated up to 12 weeks after the first treatment. In total, 84% of patients completed the trial. Mean change from baseline in facial inflammatory lesion count at 12 weeks was significantly lower in the MAL-PDT group than the placebo group (-15.6 and -7.8; p=0.006, respectively). Change in facial noninflammatory lesion count at 12 weeks did not differ significantly between groups (-11.8 vs -10.7; p=0.85). The most commonly reported adverse events were pain (n=17 [17%] in the MAL-PDT group vs 0 in the placebo group) and a skin burning cessation (n=15 [15%] in the PDT group vs 5 [9%] in the placebo group). Most adverse events were mild-to-moderate, although 12 patients in the MAL-PDT group dropped out due to treatment-related adverse events.

In a randomized, single-blind, split-faced trial, Orringer et al (2010) evaluated the efficacy of ALA-PDT in 44 patients with facial acne. For most outcomes, there were no statistically significant differences between the treated and untreated sides of the face. This included a change from baseline to 16 weeks in the mean number of inflammatory papules, pustules, cysts, closed comedones, or open comedones. There was a significantly greater reduction in erythematous macules on the treated (mean reduction, 5.9) than the untreated side of the face (mean reduction, 2.5; p=0.04). There were few adverse events, which tended to be mild. A trial limitation was the high dropout rate of 34%.

Other studies have reported higher rates of adverse events with PDT. For example, a study by Wiegell et al (2006) evaluated patients 12 weeks after MAL-PDT (n=21) or a control group (n=15). There was a 68% reduction from baseline in inflammatory lesions in the treatment group and no change in the control group (p=0.023). However, all patients experienced moderate-to-severe pain after the treatment, and 7 (33%) of 21 in the treatment group did not receive the second treatment due to pain.

**Section Summary: Acne**

Several RCTs and a Cochrane review have evaluated PDT for the treatment of acne. The review did not conduct meta-analyses on most outcomes. For the pooled analysis of studies comparing MAL-PDT and placebo, reviewers did not find a significant difference in investigator assessment of lesion change. The available RCTs have not consistently found significantly better outcomes with PDT than with comparator interventions. Several trials found that PDT was associated with high rates of adverse events leading to the cessation of treatment. Trials tended to have relatively small sample sizes and used a variety of comparison interventions.

**Other Noncancerous Dermatologic Conditions**

Clinical Context and Test Purpose
The purpose of PDT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with noncancerous dermatologic skin conditions (eg, hidradenitis suppurativa, mycoses, port-wine stain).

The question addressed in this evidence review is: Does the use of PDT improve the net health outcome for dermatologic conditions, including noncancerous dermatologic skin conditions (eg, hidradenitis suppurativa, mycoses, port-wine stain)?

The following PICO were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with noncancerous dermatologic skin conditions, including hidradenitis suppurativa, mycoses, and port-wine stain.

Patients with noncancerous dermatologic skin conditions (eg, hidradenitis suppurativa, mycoses, port-wine stain) are actively managed by dermatologists and primary care providers in an outpatient setting.

Interventions
The therapy being considered is PDT.

Comparators
The following therapies are currently being used to treat noncancerous dermatologic skin conditions: pharmacologic therapy, cryotherapy, and laser therapy.

Outcomes
The general outcomes of interest are symptoms, change in disease status, QOL, and treatment-related morbidity.

Duration of follow-up would be based on the type and extent of lesions and would typically occur in weeks to months after treatment.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined for indication 1.

Randomized Controlled Trials
Wu et al (2018) conducted a prospective, multicenter RCT involving 100 patients (age range, 16-50 years) to measure the efficacy of different dose levels of hemoporfin with PDT in treating a port-wine stain. In the trial, 40 patients received hemoporfin 2.5 mg/kg intravenously, 40 received hemoporfin 5 mg/kg intravenously, and 20 received a saline placebo. Ten minutes after infusion, all patients received PDT. After an evaluation at week 8, 75% of the high-dose group reported improvements in skin lesions compared with 40% of the low-dose group and 15% of the placebo group. Adverse events were mild and resolved within a week. Limitations included a short follow-up and small sample size.

Case Series
No controlled studies using FDA-approved photosensitizing agents for PDT in other dermatologic conditions were identified for conditions other than a port-wine stain. Only case series were identified, including series on PDT for hidradenitis suppurativa and PDT for interdigital mycoses. Most series were small (eg, <25 patients). There are a few systematic reviews. For example, a systematic review by Mostafa and Tarakji (2015) evaluated PDT for oral lichen planus identified 5 case reports, and a systematic review by Yazdani Abyaneh et al (2015) identified 15 case series (total n=223 patients) on
PDT for actinic cheilitis. Xiao et al (2011) in China published a large retrospective case series. A total of 642 patients with port-wine stains were treated with PDT; 507 were included in analyses, and the rest were excluded because they had previous lesion treatments or were lost to follow-up. After treatment, 26 (5.1%) patients were considered to have complete clearing, 48 (9.5%) had significant (<75% to <100%) clearing, and 77 (15.2%) had moderate (<50% to <75%) clearing. This single uncontrolled study is insufficient to draw conclusions about the effect of PDT on health outcomes in patients with port-wine stains.

**Section Summary: Other Noncancerous Dermatologic Conditions**

There is insufficient evidence that PDT improves the net health outcome in patients with these other dermatologic conditions (eg, hidradenitis suppurativa, mycoses, port-wine stains).

**Summary of Evidence**

For individuals who have nonhyperkeratotic AKs on the face or scalp who receive PDT, the evidence includes randomized controlled trials (RCTs). The relevant outcomes are symptoms, change in disease status, quality of life (QOL), and treatment-related morbidity. Evidence from multiple RCTs has found that PDT improves the net health outcome in patients with nonhyperkeratotic AKs on the face or scalp compared with placebo or other active interventions. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have nonhyperkeratotic AKs on the upper extremities who receive PDT, the evidence includes RCTs. The relevant outcomes are symptoms, change in disease status, QOL, and treatment-related morbidity. In two placebo-controlled RCTs, significantly more patients had a complete clearance of AKs with ALA/PDT with blue light compared to placebo at 12 weeks, and a third found a significantly greater reduction in mean lesion count at 4 weeks. Two small RCTs compared ALA/PDT using red light to imiquimod or 5-fluorouracil and found similar efficacy between the active treatment groups after six months of follow-up. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have low-risk basal cell carcinoma who receive PDT, the evidence includes RCTs and systematic reviews of RCTs. The relevant outcomes are symptoms, change in disease status, QOL, and treatment-related morbidity. Systematic reviews of RCTs have found that PDT may not be as effective as surgery for superficial and nodular basal cell carcinoma. In the small number of trials available, PDT was more effective than a placebo. The available evidence from RCTs has suggested that PDT has better cosmetic outcomes than surgery. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have squamous cell carcinoma in situ who receive PDT, the evidence includes RCTs. The relevant outcomes are symptoms, change in disease status, QOL, and treatment-related morbidity. RCTs have found that PDT has similar or greater efficacy compared with cryotherapy and 5-fluorouracil. Additionally, adverse events and cosmetic outcomes appear to be better after PDT. Few RCTs have compared PDT with surgery or radiotherapy; as a result, conclusions cannot be drawn about PDT compared with these other standard treatments. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have nonmetastatic invasive squamous cell carcinoma who receive PDT, the evidence includes observational studies and a systematic review of observational studies. The relevant outcomes are overall survival, symptoms, change in disease status, QOL, and treatment-related morbidity. Conclusions cannot be drawn from small, uncontrolled studies. RCTs are needed to
determine the safety and efficacy of PDT for this condition. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have acne who receive PDT, the evidence includes RCTs and a systematic review. The relevant outcomes are symptoms, change in disease status, QOL, and treatment-related morbidity. The available RCTs have not consistently found significantly better outcomes with PDT compared with other interventions, and a meta-analysis did not find significantly better results with PDT vs placebo. Several trials have found that PDT is associated with high rates of adverse events leading to the cessation of treatment. Trials tended to have relatively small sample sizes and used a variety of comparison interventions. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have noncancerous dermatologic skin conditions (eg, hidradenitis suppurativa, mycoses, port-wine stain) who receive PDT, the evidence includes case series, systematic reviews of uncontrolled series, and an RCT for port-wine stain. The relevant outcomes are symptoms, change in disease status, QOL, and treatment-related morbidity. RCTs are needed to determine the safety and efficacy of PDT for these conditions. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Canadian Dermatology Association

The Canadian Dermatology Association (2015) published the following recommendations on the dermatologic use of photodynamic therapy (PDT):

- Basal cell carcinoma: PDT may be used for superficial basal cell carcinoma when nonsurgical treatment is desired, there are multiple carcinomas, and when the cosmetic outcome is important. PDT is not appropriate for nodular basal cell carcinoma.\(^{45}\)
- Actinic keratosis: PDT is among the recommended treatment options for actinic keratosis, although the guidance includes the statement that cryosurgery or a surgical procedure are preferred for isolated actinic keratosis and hypertonic lesions.\(^{46}\)

National Comprehensive Cancer Network

For treatment of precancers (diffuse actinic keratoses, field cancerization), the NCCN (v.1.2020) made the following recommendations: "Accepted treatment modalities include cryotherapy, topical 5-fluorouracil (5-FU) with or without calcipotriol (calcipotriene), topical imiquimod, topical ingenol mebutate, photodynamic therapy (e.g., aminolevulinic acid, porfimer sodium), and C&E. For hyperkeratotic actinic keratoses, pretreatment with topical tazarotene, curettage, or topical keratolytics (topical urea, lactic acid, and salicylic acid) prior to above therapies may be considered."\(^{47}\)

For basal cell skin cancer, the NCCN (v.1.2020) made the following recommendations: "In patients with low-risk, superficial basal cell skin cancer, where surgery and radiation are not feasible, therapies such as topical imiquimod, topical 5-fluorouracil, photodynamic therapy (eg, aminolevulinic acid [ALA], porfimer sodium), or vigorous cryotherapy may be considered, even though the cure rates may be lower than with surgical treatment modalities."\(^{48}\)

For squamous cell skin cancers, the NCCN (v.1.2020) made the following recommendations: "In patients with SCC [squamous cell carcinoma] in situ (Bowen’s disease) alternative, therapies such as topical 5-fluorouracil, topical imiquimod, photodynamic therapy (eg, ALA, porfimer sodium), or vigorous
cryotherapy may be considered, even though the cure rates may be lower than with surgical treatment modalities."\(^47\)

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

The Centers for Medicare & Medicaid Services’ 2001 coverage policy on the treatment of actinic keratosis noted:

“Various options exist on treating AKs [actinic keratosis]. Clinicians should select an appropriate treatment based on the patient’s history, the lesion’s characteristics, and the patient’s preference for specific treatment.... Less commonly performed treatments for AKs include dermabrasion, excision, chemical peels, laser therapy, and photodynamic therapy...

Medicare covers the destruction of actinic keratosis without restrictions based on lesion or patient characteristics."\(^49\)

**Ongoing and Unpublished Clinical Trials**

Some currently ongoing and unpublished trials that might influence this review are listed in Table 10.

**Table 10. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td><strong>Ongoing</strong></td>
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<td></td>
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<tr>
<td>NCT03025724*</td>
<td>Photodynamic Therapy for Treatment of Cutaneous Squamous Cell Carcinoma in Situ</td>
<td>40</td>
<td>Jan 2020</td>
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<tr>
<td>NCT02144077</td>
<td>A Randomized, Observer Blind, Multinational Phase III Study to Evaluate the Safety and Efficacy of BF-200 ALA (Ameluz®) in Comparison to Metvix® in the Treatment of Non-aggressive Basal Cell Carcinoma (BCC) With Photodynamic Therapy (PDT)</td>
<td>281</td>
<td>Sep 2020</td>
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<tr>
<td>NCT02367547*</td>
<td>Superficial Basal Cell Cancer's Photodynamic Therapy: Comparing Three Photosensitises: Hexylaminolevulinate and Aminolevulinic Acid Nano Emulsion Versus Methylaminolevulinate</td>
<td>117</td>
<td>Dec 2022</td>
</tr>
<tr>
<td>NCT03573401*</td>
<td>A Randomized, Double-Blind, Vehicle-controlled Multicenter Phase III Study to Evaluate the Safety and Efficacy of BF-200 ALA (Ameluz®) and BF-RhodoLED® in the Treatment of Superficial Basal Cell Carcinoma (sBCC) With Photodynamic Therapy (PDT)</td>
<td>186</td>
<td>Aug 2024</td>
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<tr>
<td><strong>Unpublished</strong></td>
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<tr>
<td>NCT03511326*</td>
<td>Subject Reported Outcomes on Satisfaction, Safety and Efficacy With Luxerm® in the Field-directed Treatment of Thin or Non-hyperkeratotic and Non-pigmented Actinic Keratosis of the Face or the Scalp</td>
<td>50</td>
<td>Nov 2017 (completed)</td>
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<tr>
<td>NCT01482104</td>
<td>A Randomized Controlled Blinded Multi-centre Study of Photodynamic Therapy With Methyl-aminolevulinate Comparing a Simplified Regime With the Approved</td>
<td>277</td>
<td>Oct 2017 (completed)</td>
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Dermatologic Applications of Photodynamic Therapy

Regime in Patients With Clinical Low-risk Superficial and Nodular Basal Cell Carcinoma.

NCT02685592 Photodynamic Therapy for Lentigo Maligna Using 5-aminolevulinic Acid Nanoemulsion as a Light Sensitizing Cream (LM PDT) 10 Mar 2018 (completed)

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

**ESSENTIAL HEALTH BENEFITS**

The Affordable Care Act (ACA) requires fully insured non-grandfathered individual and small group benefit plans to provide coverage for ten categories of Essential Health Benefits (“EHBs”), whether the benefit plans are offered through an Exchange or not. States can define EHBs for their respective state.

States vary on how they define the term small group. In Idaho, a small group employer is defined as an employer with at least two but no more than fifty eligible employees on the first day of the plan or contract year, the majority of whom are employed in Idaho. Large group employers, whether they are self-funded or fully insured, are not required to offer EHBs, but may voluntarily offer them.

The Affordable Care Act requires any benefit plan offering EHBs to remove all dollar limits for EHBs.

**REFERENCES**


15. Yazdanyar S, Zarchi K, Jemec GBE. Pain during topical photodynamic therapy - comparing methyl aminolaevulinate (Metvix(R)) to aminolaevulinic acid (Ameluz(R)); an intra-individual clinical study. Photodiagnosis Photodyn Ther. Aug 02 2017. PMID 28780136
18. Taub AF, Garretson CB. A randomized, blinded, bilateral intraindividual, vehicle-controlled trial of the use of photodynamic therapy with 5-aminolevulinic acid and blue light for the treatment of actinic keratoses of the upper extremities.. J Drugs Dermatol, 2011 Nov 5;10(9). PMID 22052276
19. Sotiriou E, Apalla Z, Maliamani F et al. Intraindividual, right-left comparison of topical 5-aminolevulinic acid photodynamic therapy vs. 5% imiquimod cream for actinic keratoses on the upper extremities.. J Eur Acad Dermatol Venereol, 2009 May 28;23(9). PMID 19470041
34. Xu X, Zheng Y, Zhao Z et al. Efficacy of photodynamic therapy combined with minocycline for treatment of moderate to severe facial acne vulgaris and influence on quality of life.. Medicine (Baltimore), 2018 Feb 3;96(51). PMID 29390528


**CODES**

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<td>Photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitive drug(s), per day. (use for reporting when physician or other qualified health care professional is not directly involved in the delivery of the service)</td>
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<tr>
<td></td>
<td>96573</td>
<td>Photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitive drug(s), per day. (use for reporting when physician or other qualified health care professional is not directly involved in the delivery of the service)</td>
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</table>
illuminatio/activityon of photosensitizing drug(s) provided by a physician or
other qualified health care professional, per day

96574 Debridement of premalignant hyperkeratotic lesion(s) (ie, targeted curettage,
abrasion) followed with photodynamic therapy by external application of light to
destroy premalignant lesions of the skin and adjacent mucosa with application
and illumination/activityon of photosensitizing drug(s) provided by a physician or
other qualified health care professional, per day

HCPCS
J7308 Aminolevulinic hydrochloric acid for topical administration, 20%, single unit
dosage form (354 mg)

J7309 Methyl aminolevulinate (MAL) for topical administration, 16.8%, 1 gram

ICD-
10-CM
B36.8-
B36.9;
B48.8-B49
C44.0-
C44.99
D04.0-
D04.9
L57.0
L70.0
L73.2
Q82.5
ICD-
10-PCS
ICD-
10-PCS codes are only used for inpatient services.

6A600ZZ;
6A601ZZ
Extracorporeal therapies, physiological systems, phototherapy skin, codes for
single and multiple

Type
of
Service
Medicine
Place
of
Service
Physician’s
office

POLICY HISTORY

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<td>01/09/14</td>
<td>Replace policy</td>
<td>Literature update through December 2, 2013. References 6, 13, 17, 20, and 23 added; other references renumbered or removed. Policy statements unchanged.</td>
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<td>01/15/15</td>
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<td>Policy updated with literature review through December 15, 2014; references 3, 7-10, and 12 added and reference 30 updated. In medically necessary statement, superficial basal cell carcinoma changed to low-risk (ie, superficial or nodular) basal cell carcinoma. In investigational statement, non-superficial basal cell carcinoma changed to high-risk basal cell carcinoma.</td>
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### Dermatologic Applications of Photodynamic Therapy

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