Photodynamic Therapy for the Treatment of Actinic Keratoses and Other Skin Lesions

I. Description

Photodynamic therapy (PDT) refers to light activation of a photosensitizer to generate highly reactive intermediaries, which ultimately cause tissue injury and necrosis. Photosensitizing agents, administered orally or intravenously, have been used in nondermatologic applications and are being proposed for use with dermatologic conditions such as actinic keratosis and nonmelanoma skin cancers.

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

The evidence for PDT in individuals who have low-risk basal cell carcinoma (BCC) includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. Systematic reviews of RCTs have found that PDT may not be as effective as surgery for superficial and nodular BCC. These systematic reviews have not found statistically significant differences in clinical response rates with PDT compared with cryotherapy for BCC, which suggests, but does not conclusively demonstrate, similar efficacy. Cosmetic outcomes have been better after PDT than after surgery or cryotherapy. In the small number of trials available, PDT was more effective than placebo. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for PDT in individuals who have squamous cell carcinoma in situ includes RCTs. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. RCTs have found that PDT has similar or greater efficacy compared with cryotherapy and
5-fluorouracil. Additionally, adverse events/cosmetic outcomes appeared to be better after PDT. Few RCTs compare 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for PDT in individuals who have nonmetastatic invasive squamous cell carcinoma includes observational studies and a systematic review of observational studies. Relevant outcomes are overall survival, symptoms, change in disease status, quality of life, 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.

The evidence for PDT in individuals who have acne includes RCTs and other controlled trials. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. Several small (ie, <50 patients) randomized and nonrandomized studies have evaluated PDT for treatment of acne. These studies tended to find that PDT was at least as effective as a control condition. Some studies have reported higher rates of adverse events associated with PDT therapy, while others have not. A limitation of this body of evidence is that few studies have evaluated PDT as the sole intervention; therefore, more data are needed that isolate the impact of PDT before conclusions can be drawn about the efficacy of this therapy for treating acne. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for PDT in individuals who have conditions such as hidradenitis suppurativa, mycoses, or port wine stains includes case series and systematic reviews of uncontrolled series. Relevant outcomes are symptoms, change in disease status, quality of life, 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.

II. Criteria/Guidelines

A. Photodynamic therapy is covered (subject to Limitations and Administrative Guidelines) for the treatment of:
   1. Nonhyperkeratotic actinic keratoses of the face and scalp
   2. Low-risk (e.g., superficial and nodular) basal cell skin cancer only when surgery and radiation are contraindicated
   3. Bowen disease (squamous cell carcinoma in situ) only when surgery and radiation are contraindicated.

Surgery or radiation is the preferred treatment 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 in comparison with 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.

III. Limitations

A. Photodynamic therapy is not covered for the treatment of other dermatologic applications, including but not limited to, acne vulgaris, high-risk basal cell carcinomas, hidradenitis suppurativa, and mycoses, due to the lack of scientific evidence demonstrating improved health outcomes.

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

IV. Administrative Guidelines

Precertification is not required for this service. Documentation supporting the medical necessity should be legible, maintained in the patient's medical record and must be made available to HMSA upon request. HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria.

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<td>Photodynamic therapy by external application of light to destroy premalignant and/or malignant lesions of the skin and adjacent mucosa (e.g. lip) by activation of photosensitive drug(s), each phototherapy session</td>
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<td>J7308</td>
<td>Aminolevulinic acid HCl for topical administration, 20%, single unit dosage form (354 mg)</td>
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<td>J7309</td>
<td>Methyl aminolevulinate (MAL) for topical administration, 16.8%, 1 gram</td>
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V. Scientific 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 (MAL). When applied topically, these agents pass readily through abnormal keratin overlying the lesion and accumulate preferentially in dysplastic cells. 5-ALA and MAL are metabolized by underlying cells to photosensitizing concentrations of porphyrins. Subsequent exposure to photoactivation (maximum absorption at 404-420 nm and 635 nm, respectively) 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. It has also been investigated as a treatment of other superficial dermatologic lesions, such as Bowen disease, acne vulgaris, mycoses, hidradenitis suppurativa, and superficial and nodular basal cell carcinoma (BCC). Potential cosmetic indications include skin rejuvenation and hair removal.

Actinic keratoses are rough, scaly, or warty premalignant growths on 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, actinic keratosis may progress to squamous cell carcinoma (SCC). Available treatments for actinic keratoses can generally be divided into surgical and nonsurgical methods. Surgical treatments used to treat 1 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 imiquimod creams), chemexfoliation (also known as 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 different treatment methods may be used.

Nonmelanoma skin cancers are the most common malignancies in the white population. BCC is the most found in light-skinned people and 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. Bowen disease is an SCC in situ with the potential for significant lateral spread. Metastases are rare, with less than 5% of cases advancing to invasive SCC. Lesions may appear on sun-exposed or covered skin. 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. Poor cosmesis resulting from surgical procedures and skin irritation induced by topical agents can be significant problems.
Photodynamic Therapy for the Treatment of Actinic Keratoses and Other Skin Lesions

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 following indication: “The Levulan Kerastick for topical solution plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy Illuminator is indicated for the treatment of nonhyperkeratotic actinic keratoses of the face and scalp.” The product is applied in the physician’s office. FDA product code: MVF

A 5-aminolevulinic acid patch technology (5-ALA Patch) is available outside of the U.S through an agreement between Intendis (part of Bayer HealthCare) and Photonamic. The 5-ALA patch is not approved by FDA.

Another variant of photodynamic therapy (PDT) for skin lesions is Metvixia® used with the Aktilite CL128 lamp, each of which received FDA approval in July 2004. Metvixia® (Galderma, Switzerland; PhotoCure, Norway) consists of the topical application of methyl aminolevulinate (in contrast to ALA used in the Kerastick procedure) followed by exposure with the Aktilite CL 128 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 non-hyperkeratotic actinic keratoses of the face and scalp in immunocompetent patients when used in conjunction with lesion preparation (débridement 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 2001 and has been updated regularly with searches of the MEDLINE database. Most recently, the literature was reviewed through December 6, 2015. Key literature is described next and focuses on studies evaluating U.S. Food and Drug Administration (FDA) –approved photosensitizing agents.

Actinic Keratoses

Efficacy of photodynamic therapy compared with placebo
Several randomized controlled trials (RCTs) have been published. For example, in 2003, Pariser et al conducted a randomized, placebo-controlled trial of 80 patients with actinic keratoses. The authors reported that the complete response (CR) rate for the methyl aminolevulinate (MAL) group was 89% compared with 38% in the placebo group.

A 2009 double-blind RCT conducted in Germany by Hauschild et al evaluated photodynamic therapy (PDT) with 5-aminolevulinic acid (5-ALA) using a self-adhesive patch. Eligibility criteria included Caucasian patients, age 18 years and older with skin type I-IV (pale to olive complexion) and actinic keratoses on the head and of mild or moderate grade, as defined by Cockerell
Patients were randomly assigned to receive 5-ALA patches containing 8 mg 5-ALA or identical placebo patches. Patches were square, measuring 4 cm², and patients received 3 to 8 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.

**Efficacy of PDT compared with alternative intervention**

A number of published RCTs compare PDT with other therapies, and a systematic review of these studies has been published. Patel et al (2014) reviewed RCTs with at least 10 patients that addressed the efficacy of topical PDT compared with an alternative (ie, non-PDT) treatment of actinic keratosis. A total of 13 studies with 641 participants met the review’s inclusion criteria. Studies compared PDT with cryotherapy (n=6), fluorouracil (n=2), imiquimod (n=4), and carbon dioxide laser (n=1). Seven studies used ALA and the other 6 used MAL as the PDT sensitizer. Most studies focused on lesions located on the face or scalp. No studies in the review was double-blind.

In 12 of the 13 studies, primary outcome was a measure related to the clearance rate of lesions. Data from 4 RCTs comparing PDT and 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.

Representative RCTs are described next.

In 2006, Morton et al published an industry-sponsored, 25-center, randomized, left-right comparison of single PDT and cryotherapy in 119 subjects with actinic keratoses on the face or scalp. At 12-week follow-up, PDT resulted in a significantly higher rate of cured lesions compared with cryotherapy (86.9% vs 76.2%, respectively, cured). Lesions with a non-CR were retreated after 12 weeks; a total of 108 (14.9%) of 725 lesions received a second PDT session; 191 (26.8%) of 714 lesions required a second cryotherapy treatment. At 24 weeks, groups showed equivalent clearance (85.8% vs 82.5%, respectively). Skin discomfort was reported to be greater with PDT than with cryotherapy. Investigator-rated cosmetic outcomes showed no difference in the percentage 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.

In 2010, Szeimies et al in Germany reported 12-month follow-up data from a study comparing PDT using a self-adhesive patch to cryotherapy. The study had the same eligibility criteria and primary outcome as the Hauschild et al study, previously described. A total of 148 patients were randomly assigned to the 5-ALA patch group, 49 to a placebo group, and 149 to a cryotherapy group. The study used a test of noninferiority of PDT versus cryosurgery. Fourteen patients who dropped out were excluded from the analysis comparing PDT and cryotherapy. The rate of complete clearance of all lesions was 67% (86 of 129) in the 5-ALA group, 52% (66 of 126) in the cryosurgery group,
and 12% (5 of 43) in the placebo group. Clearance rate was significantly higher in the 5-ALA patch group than 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 up for an additional 9 months; 316 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 compared with placebo (in both studies) and in cryosurgery (in the second study). Thirty-two percent 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. The corresponding figure 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, but no serious adverse effects due to study intervention were documented. PDT patches used in the German studies have not been cleared by FDA for use in the United States.

A 2012 randomized pilot study from Spain compared PDT using MAL alone, imiquimod alone, and the combination of the 2 treatments. Patients with nonhyperkeratotic actinic keratoses on the face and/or scalp were randomly assigned 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) PDT, as above, followed by 4 weeks of imiquimod cream (n=32). Follow-up occurred 1 month after PDT (group 1) or 1 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 actinic keratoses 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 limitation of the study was that the PDT-only group was followed for a shorter amount of time, which could at least partially explain the lower rate of CR.

**Efficacy of different PDT protocols**

Several RCTs have compared different approaches to applying PDT in the treatment of actinic keratoses. No clear evidence of superiority of one approach over another emerges from this body of evidence, and some of the alternative approaches (e.g., daylight PDT) are not FDA-cleared.

**Section Summary**

Evidence from multiple RCTs has found that PDT improves the net health outcome in patients with nonhyperkeratotic actinic keratoses on the face or scalp compared with placebo or other active interventions. There is insufficient evidence that any PDT protocol is superior to any other protocol.

**Basal Cell Carcinoma**

A 2007 Cochrane review evaluated surgical, destructive (including PDT), and chemical interventions for basal cell carcinoma (BCC). The authors concluded that surgery and radiotherapy appeared to be the most effective treatments, with the best results obtained with surgery. In addition, they stated that cosmetic outcomes appear to be good with PDT, but additional data with long-term follow-up are needed. The Cochrane review did not distinguish among BCC subtypes.
More recently, in 2015, Wang et al published a meta-analysis of RCTs on PDT for treating BCC, both superficial and nodular. To be included in the systematic review, studies needed to include adults with 1 or more primary BCCs, randomize participants to PDT versus placebo or another treatment and report the complete clearance rate, recurrence rate, cosmetic outcomes, and/or adverse events. A total of 8 RCTs with 1583 patients, published between 2001 and 2013, met inclusion criteria. Three trials included patients with superficial BCC, 3 included patients with nodular BCC, and 1 included patients with both types of low-risk BCC. Four trials compared PDT and surgery, 2 compared PDT and cryotherapy, 1 compared PDT and pharmacologic treatment, and 1 was placebo controlled.

In meta-analysis of 7 studies, the estimated probability of complete clearance after treatment was similar in the PDT and 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 when compared with placebo. In a pooled subgroup analyses by tumor type, results were similar except that the upper CI for nodular BCC just crossed 1.00 and was thus not statistically significant, and the upper CI for superficial BCC was just below 1 and thus was statistically significant (RR=0.93; 95% CI, 0.85 to 1.01) and the upper CI for superficial BCC was just below 1.00 and thus was statistically significant (RR=0.93; 95% CI, .088 to 0.98). Only 1 study on superficial BCC contributed data to this subgroup analysis.

When data from 6 studies were pooled, there was no statistically significant difference in the recurrence rate at 1 year in the PDT and non-PDT groups. 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 compared 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 2012 systematic review by Roozeboom et al focused only on superficial BCC and included both randomized and nonrandomized trials. Sixteen studies identified evaluated PDT for treating BCC; 6 studies were RCTs. There was significant heterogeneity among studies ($I^2=94\%$, $p<0.001$). A pooled estimate of CR after treatment with PDT in 13 studies (PDT arms only) was 79% (95% CI, 71% to 87%). In 3 studies that compared illumination regimens, only 1 arm was included, and in 2 studies that compared PDT agents, both arms were included.

Representative RCTs are described next.

An industry-sponsored multicenter RCT was published in 2008 by Szeimies et al. The trial compared with MAL-PDT with surgery for small (8–20 mm) superficial BCC in 196 patients. At 3 months after treatment, 92% of lesions treated with MAL-PDT showed clinical response, compared with 99% of lesions treated with surgery (per protocol analysis). At 12-month follow-up, no lesions had recurred in the surgery group, and 9% of lesions had recurred with MAL-PDT. Approximately 10% of patients discontinued MAL-PDT due to an incomplete response or adverse
event, as 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.

In 2007, Rhodes et al published 5-year follow-up of an industry-sponsored multicenter randomized study comparing MAL-PDT with surgery for nodular BCC. A total of 101 adults with previously untreated nodular BCC were randomized to receive MAL therapy or surgery. At 3 months, CR rates did not differ between the 2 groups; however, at 12 months, CR rate had fallen from 91% to 83% in the MAL-PDT group, while in the surgery group, the CR rate had fallen from 98% to 96%. Of 97 patients in the per protocol population, 66 (68%) were available for 5-year follow-up; 16 (32%) discontinued in the MAL-PDT group due to treatment failure or adverse events versus 6 (13%) in the surgery group. A time-to-event analysis of lesion response over time 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 54% of the surgery patients.

An observational study published in 2011 by Lindberg-Larsen provides additional data on recurrence rates after treatment with PDT. The study included 90 patients with 157 lesions (n=111 superficial BCC, n=40 nodular BCC, and n=6 unknown) who were initially treated with MAL-PDT. Each lesion was treated twice, with 1 week between treatments. The authors did not report the initial rate of clinical response. Recurrence was defined as reappearance of a histologically verified BCC in a previously affected area. Estimated recurrence rate was 11% at 6 months, 16% at 12 months, and 19% at 24 months. There was a significantly higher rate of recurrence for nodular BCC than superficial BCC (e.g., at 12 months, recurrence rates were 28% and 13%, respectively, p=0.008). Although this study found higher rates of recurrence for nodular versus superficial BCC, it was not randomized and, thus, may have had confounding factors. For example, the authors noted that nodular BCCs were more frequently located on patients with fewer tumors and that patients with more tumors had a lower risk of recurrence. In addition, the number of nodular BCCs was relatively small and findings may not be robust.

**Section Summary**

Systematic reviews of RCTs have found that PDT does not appear to be as effective as surgery for superficial and nodular BCC. These systematic reviews have not found statistically significant differences in clinical response rates with PDT compared with cryotherapy for BCC, which suggests, but does not conclusively demonstrate, similar efficacy. Cosmetic outcomes have been better after PDT compared with surgery and cryotherapy. In the small number of trials available, PDT was more effective than placebo.

**Squamous Cell Carcinoma In Situ (Bowen Disease)**

Bath-Hextall et al published a Cochrane review of interventions for cutaneous Bowen disease in 2013. Investigators identified 7 RCTs evaluating PDT; 4 of these compared 2 PDT protocols, 1 compared PDT with cryotherapy, 1 compared PDT with topical 5-fluorouracil (5-FU), and 1 compared PDT with both PDT and 5-FU. The authors did not pool study results.
The largest study (n=225) was a 3-arm trial published in 2006 by Morton et al. This was a multicenter study conducted in 11 European countries. A total of 225 patients were randomized to receive 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%, 86%, 83%, respectively) at 3 months and superior to cryotherapy and 5-FU (80% vs 67% vs 69%, respectively) at 12 months. Cosmetic outcome at 3 months was rated higher for PDT than the standard nonsurgical treatments by both investigators and blinded evaluators, with investigators rating cosmetic outcome 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 in 2003. Forty patients were randomly assigned to undergo either 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 7 lesions, ulceration in 3, and erosions in 2. No such reactions were noted in the PDT group.

**Section Summary**

RCTs have found that PDT has similar or greater efficacy compared with cryotherapy and 5-FU for patients with Bowen disease. Additionally, adverse effects/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**

In 2013, Lansbury et al published a systematic review of observational studies evaluating interventions for nonmetastatic cutaneous squamous cell carcinoma (SCC). Investigators identified 14 prospective studies evaluating PDT. Sample sizes ranged from 4 to 71 patients, and only 3 studies included more than 25 patients. These studies evaluated various PDT protocols. There was only 1 comparative study, and it compared 2 different PDT regimens. In meta-analysis, a mean of 72% of lesions had a CR to treatment (95% CI, 61.5% to 81.4%; $I^2=71$%). Eight studies addressed recurrence rates in patients who were initial responders. In meta-analysis, pooled odds of recurrence was 26.4% (95% CI, 12.3% to 43.7%; $I^2=72$%).

**Section Summary**

No RCTs evaluating PDT for treatment of nonmetastatic invasive SCC 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**

Several RCTs and other controlled trials have been published. A randomized, single-blind, split-faced trial was published in 2010 by Orringer et al in the United States. The trial included 44 patients with facial acne. A randomly selected side of the face received the intervention
(combined treatment with topical 5-ALA and pulsed dye laser [PDL]) and the other side of the face went untreated. Patients received up to 3 treatments at intervals of approximately 2 weeks. Twenty-nine patients (66%) completed the 16-week study. For most outcomes, there were no statistically significant differences between treated and untreated sides of the face. This included change from baseline to 16 weeks in mean number of inflammatory papules, pustules, cysts, closed comedones, or open comedones. There was a significantly greater reduction in erythematous macules on the treated compared with the untreated side of the face (a mean reduction of 5.9 and 2.5, respectively; \( p=0.04 \)). In addition, improvement in mean Leed’s Acne Severity Grading score was significantly greater on the treated side of the face (-1.07) compared with the untreated side (-0.52) (\( p=0.001 \)). There were few adverse effects, which tended to be mild. A limitation of the study was the high dropout rate.

In 2012, Shaaban et al in Egypt published a nonrandomized split-faced study of 30 patients with inflammatory and nodulocystic acne. In each patient, the right side was treated with a monthly session of ALA-PDT plus intense pulsed-light (IPL) treatment, and the left side was treated with IPL only. From baseline to 1-month follow-up, mean count (SD) of facial acne lesions decreased from 9.55 (1.1) to 2.1 (1.68) in the combined treatment group, and from 9.8 (4.8) to 5.01 (1.7) in the IPL-only group. The difference in lesion count between groups was statistically significant. Limitations of the study were lack of randomization and inclusion of a group that received PDT as the sole intervention.

In 2013, Mei et al in China published a parallel-group RCT of 41 patients with moderate-to-severe facial acne. The trial evaluated the additional value of ALA PDT in patients treated with IPL. Twenty-one patients were randomized to 4 weeks of treatment with IPL plus PDT, and 20 patients were randomized to IPL plus placebo PDT. Mean reduction in both inflammatory and noninflammatory lesions was significantly greater in the IPL plus PDT group than in the IPL-only group at the 4-, 8-, and 12-week follow-ups. For example, in the IPL plus PDT group, the mean number (SD) of noninflammatory acne lesions decreased from 31.3 (7.1) at baseline to 14.0 (6.2) at 12-week follow-up. In the IPL-only group, the mean number (SD) of noninflammatory lesions decreased from 28.2 (4.1) at baseline to 18.6 (3.1) at 12 weeks (\( p<0.05 \)). An improvement of 75% to 100% in all lesions was attained by 13 patients (62%) in the IPL plus PDT group and by 3 patients (15%) in the IPL-only group. Both treatments were well tolerated, and no patient withdrew from the trial due to adverse effects of treatment. The trial did not evaluate the efficacy of PDT in the absence of IPL therapy.

In some studies, a higher rate of adverse events with PDT has been reported. For example, a 2006 study by Wiegell et al in Denmark 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 treatment and 7 (33%) of 21 in the treatment group did not receive the second treatment due to pain.

Section Summary
Several small (i.e., <50 patients) randomized and nonrandomized studies have evaluated PDT for treatment of acne. These studies tended to find that PDT was at least as effective as a control condition. Some studies have reported higher rates of adverse effects associated with PTD therapy, but others have not. A limitation of this body of evidence is that there are few studies evaluating PDT as the sole intervention; therefore, more data are needed that isolate the impact of PDT before conclusions can be drawn about the efficacy of this therapy for treating acne.

**Other dermatologic indications**
No controlled studies using FDA-approved photosensitizing agents for PDT in other dermatologic indications were identified. Only case series were identified, including series on PDT for hidradenitis suppurativa and PDT for interdigital mycoses. Most series had small sample sizes (eg, <25 patients). There were a few systematic reviews. For example, a 2015 systematic review by Mostafa and Tarakji of studies evaluating PDT for oral lichen planus identified 5 case reports and a 2015 systematic review by Yazdani Abyaneh et al identified 15 case series (total N=223) on PDT for actinic cheilitis. In 2011, Xiao et al 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 the study, and the rest were excluded because they had had previous lesion treatments or had been lost to follow-up. After treatment, 26 patients (5.1%) 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**
There is insufficient evidence that PDT improves the net health outcome in patients with these miscellaneous dermatologic conditions (eg, hidradenitis suppurativa, mycoses, port wine stains).

**Ongoing and Unpublished Clinical Trials**
A search of ClinicalTrials.gov in December 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

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

The evidence for PDT in individuals who have low-risk basal cell carcinoma (BCC) includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. Systematic reviews of RCTs have found that PDT
may not be as effective as surgery for superficial and nodular BCC. These systematic reviews have not found statistically significant differences in clinical response rates with PDT compared with cryotherapy for BCC, which suggests, but does not conclusively demonstrate, similar efficacy. Cosmetic outcomes have been better after PDT than after surgery or cryotherapy. In the small number of trials available, PDT was more effective than placebo. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for PDT in individuals who have squamous cell carcinoma in situ includes RCTs. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. RCTs have found that PDT has similar or greater efficacy compared with cryotherapy and 5-fluorouracil. Additionally, adverse events/cosmetic outcomes appeared to be better after PDT. Few RCTs compare 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for PDT in individuals who have nonmetastatic invasive squamous cell carcinoma includes observational studies and a systematic review of observational studies. Relevant outcomes are overall survival, symptoms, change in disease status, quality of life, 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.

The evidence for PDT in individuals who have acne includes RCTs and other controlled trials. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related morbidity. Several small (ie, <50 patients) randomized and nonrandomized studies have evaluated PDT for treatment of acne. These studies tended to find that PDT was at least as effective as a control condition. Some studies have reported higher rates of adverse events associated with PDT therapy, while others have not. A limitation of this body of evidence is that few studies have evaluated PDT as the sole intervention; therefore, more data are needed that isolate the impact of PDT before conclusions can be drawn about the efficacy of this therapy for treating acne. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for PDT in individuals who have conditions such as hidradenitis suppurativa, mycoses, or port wine stains includes case series and systematic reviews of uncontrolled series. Relevant outcomes are symptoms, change in disease status, quality of life, 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.

Practice Guidelines and Position Statements

Canadian Dermatology Association
In 2015, the Canadian Dermatology Association published the following recommendations on
dermatologic use of PDT:

- Basal cell carcinoma: PDT may be used for superficial BCC when nonsurgical treatment is desired, there are multiple carcinomas, and when cosmetic outcome is important. PDT is not appropriate for nodular BCC.
- 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.

National Comprehensive Cancer Network
The clinical practice guideline on basal cell skin cancers (v.1.2016) from the National Comprehensive Cancer Network (NCCN) states: “Since cure rates may be lower, superficial therapies should be reserved for those patients where surgery or radiation is contraindicated or impractical. Superficial therapies include topical treatment with 5-FU [5-fluorouracil] or imiquimod, photodynamic therapy (PDT) and cryotherapy.” Moreover, the guideline describes BCC histologic subtypes that have low risk of recurrence as nodular, superficial, and other nonaggressive growth patterns, such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus. For patients with low-risk BCCs, the guideline states, “…topical therapies such as 5-FU (5-fluorouracil), imiquimod, PDT (eg, porfimer sodium or topical amino levulinic acid) or vigorous cryotherapy may be considered even though the cure rate may be lower.”

British Association of Dermatologists
In 2008, the British Association of Dermatologists published guidelines containing the following statement on PDT:

Multicentre randomized controlled studies now demonstrate high efficacy of topical photodynamic therapy (PDT) for actinic keratoses, Bowen's disease (BD) and superficial basal cell carcinoma (BCC), and efficacy in thin nodular BCC, while confirming the superiority of cosmetic outcome over standard therapies. Long-term follow-up studies are also now available, indicating that PDT has recurrence rates equivalent to other standard therapies in BD and superficial BCC, but with lower sustained efficacy than surgery in nodular BCC. In contrast, current evidence does not support the use of topical PDT for squamous cell carcinoma.... There is an accumulating evidence base for the use of PDT in acne, while detailed study of an optimized protocol is still required.

International Society for Photodynamic Therapy in Dermatology
The International Society for Photodynamic Therapy in Dermatology (ISPTD) published consensus-based guidelines on the use of PDT for nonmelanoma skin cancer in 2005. Based on both efficacy and cosmetic outcome, ISPTD recommended PDT as a first-line therapy for actinic keratosis. The guideline authors considered ALA not to have sufficient tissue penetration for nodular BCC. Based on 2 randomized controlled and 3 open-label studies, it was concluded that MAL-PDT can be effective for nodular BCC lesions less than 2 mm in depth, if debulked. The
guideline recommended PDT for superficial BCC as “a viable alternative when surgery would be inappropriate or the patient or physician wishes to maintain normal skin appearance.” The guideline concluded that PDT is at least as effective as cryotherapy or 5-FU for Bowen disease but that there is insufficient evidence to support the routine use of topical PDT for squamous cell carcinoma.

**Medicare National Coverage**

Centers for Medicare and Medicaid Services coverage policy on treatment of actinic keratosis dated November 26, 2001, notes:

Various options exist on treating 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 actinic keratosis 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.

**VI. Important Reminder**

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician. Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

**VI. References**


