

## Appendix D

Examples of Private Payor Coverage for Inflammatory Diseases states in addition to psoriasis

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## Medical Policy



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**\*Current Policy Effective Date: 9/1/24**  
(See policy history boxes for previous effective dates)

## **Title: Light and Laser Therapy for Vitiligo and Atopic Dermatitis**

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### **Description/Background**

#### **Vitiligo**

Vitiligo is an idiopathic skin disorder that causes depigmentation of sections of skin, most commonly on the extremities. Depigmentation occurs because melanocytes are no longer able to function properly. The cause of vitiligo is unknown; it is sometimes considered to be an autoimmune disease. The most common form of the disorder is non-segmental vitiligo in which depigmentation is generalized, bilateral, symmetrical, and increases in size over time. In contrast, segmental vitiligo, also called asymmetric or focal vitiligo, covers a limited area of skin. The typical natural history of vitiligo involves stepwise progression with long periods in which the disease is static and relatively inactive, and relatively shorter periods in which areas of pigment loss increase.

#### **Atopic Dermatitis**

Atopic dermatitis (AD), or atopic eczema, is a chronic skin condition characterized by a dry, itchy rash on the face, elbows, hands, knees, and/or feet. In addition to skin care and avoidance of substances that might irritate the skin, topical ointments and creams, and oral corticosteroid are standard treatment options.

The pathophysiology of AD involves the complex interaction between genetic and environmental factors, which lead to changes in immunoregulation and disruption of the skin barrier. The goal of conventional AD management is to reduce the frequency and severity of flares.

First-line management of AD includes patient education, avoidance of triggering factors, hydration, treatment of flares through anti-inflammatory pharmacologic therapy and nonpharmacologic therapies aimed at compensation of the skin barrier defects.

Phototherapy and photochemotherapy (i.e., UVA, UVB and PUVA) are considered second-line modalities. Given that traditional therapies may not be effective and carry long-term side effects, artificial ultraviolet radiation has been investigated as a treatment adjunct or alternative to conventional treatments.

## **Treatment**

There are numerous medical and surgical treatments aimed at decreasing disease progression and/or attaining repigmentation. Topical corticosteroids, alone or in combination with topical vitamin D<sub>3</sub> analogs, is a common first-line treatment for vitiligo. Alternative first-line therapies include topical calcineurin inhibitors, systemic steroids, and topical antioxidants. Treatment options for vitiligo recalcitrant to first-line therapy include, among others, light box therapy with ultraviolet B (UVB) and psoralen plus ultraviolet A (PUVA).

Targeted phototherapy with handheld lamps or lasers is also being evaluated. Potential advantages of targeted phototherapy include the ability to use higher treatment doses and to limit exposure to surrounding tissue. Original ultraviolet B devices consisted of a Phillips TL-01 fluorescent bulb with a maximum wavelength ( $\lambda_{\text{max}}$ ) of 311 nm. Subsequently, xenon chloride lasers and lamps were developed as targeted ultraviolet B treatment devices; these devices generate monochromatic or very narrowband radiation with a  $\lambda_{\text{max}}$  of 308 nm. Targeted phototherapy devices are directed at specific lesions or affected areas, thus limiting exposure to the surrounding normal tissues. They may, therefore, allow higher dosages compared with a light box, which could result in fewer treatments.

PUVA uses a psoralen derivative in conjunction with long-wavelength ultraviolet A (UVA) light (sunlight or artificial) for photochemotherapy of skin conditions. Psoralens are tricyclic furocoumarins that occur in certain plants and can also be synthesized. They are available in oral and topical forms. Oral PUVA is generally given 1.5 hours before exposure to UVA radiation. Topical PUVA therapy refers to direct application of psoralen to the skin with subsequent exposure to UVA light. With topical PUVA, UVA exposure is generally administered within 30 minutes of psoralen application. No topical psoralen formulation is currently available in the US.

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## **Regulatory Status**

In 2001, XTRAC™ (PhotoMedex), a xenon chloride (XeCl) excimer laser, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for the treatment of skin conditions such as vitiligo. The 510(k) clearance has subsequently been obtained for a number of targeted UVB lamps and lasers, including newer versions of the XTRAC system including the XTRAC Ultra™, the VTRAC™ lamp (PhotoMedex), the BClear™ lamp (Lumenis), the 308-excimer lamp phototherapy system (Quantel Medical) and the Excilite™ and Excilite  $\mu$ ™ XeCl lamps. The intended use of all of these devices includes vitiligo among other dermatologic indications. Some of the light-emitting devices are handheld. FDA product code: GEX.

The oral psoralen products methoxsalen soft gelatin capsules (previously available under the brand name Oxsoralen Ultra), has been approved by the FDA.

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## Medical Policy Statement

Psoralen plus ultraviolet A (PUVA), narrowband ultraviolet B (NB-UVB), and targeted phototherapy with excimer laser, with or without the use of oral or topical medications for the treatment of vitiligo are considered established treatments. They may be useful therapeutic options when indicated.

Phototherapy and photochemotherapy (i.e., ultraviolet A [UVA], UVB and PUVA) are considered established treatments with severe cases of atopic dermatitis, contact dermatitis and other eczema when criteria are met.

Home ultraviolet B (UVB) light therapy is considered established for any one of the following diagnoses:

- Atopic dermatitis when topical treatment alone has failed; **or**
- Pityriasis lichenoides; **or**
- Pruritus of hepatic disease; **or**
- Pruritus of renal failure; **or**
- Psoriasis, when topical treatment alone has failed; **or**
- Cutaneous T-cell lymphoma including mycosis fungoides and Sézary syndrome.

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## Inclusionary and Exclusionary Guidelines

### Inclusions:

Psoralen plus ultraviolet A (PUVA), narrowband ultraviolet B (NB-UVB), and targeted phototherapy with excimer laser, with or without the use of oral or topical medications for the treatment of vitiligo are considered established treatments for the following:

- Vitiligo that is not responsive to other forms of conservative therapy (e.g., topical corticosteroids, coal/tar preparations).
- NB-UVB and excimer laser phototherapy in individuals  $\geq 3$  years of age.
- Topical PUVA can be performed in children  $\geq 2$  years of age when up to 20% of their body surface area is affected.
- Systemic PUVA or oral PUVA is restricted to children  $> 12$  years who have widespread vitiligo ( $\geq 20\%$  body surface area).
- Treatment of vitiligo is restricted to the face, neck, trunk, and extremities.

Phototherapy and photochemotherapy (i.e., ultraviolet A [UVA], UVB and PUVA) are considered established treatments with severe cases of atopic dermatitis, contact dermatitis and other eczema when criteria are met:

- PUVA and NB-UVB for severe atopic dermatitis, contact dermatitis or eczema not responding to first-line therapy

Home ultraviolet light booth UVB phototherapy is considered established when conditions A and B are met:

A. The treatment is for one of the following conditions:

1. Atopic dermatitis when topical treatment alone has failed; **or**
2. Pityriasis lichenoides; **or**
3. Pruritus of hepatic disease; **or**
4. Pruritus of renal failure; **or**
5. Psoriasis, when topical treatment alone has failed; **or**
6. Cutaneous T-cell lymphoma including mycosis fungoides and Sézary syndrome.

**and**

B. The treatment meets **all** of the following criteria:

1. Treatment is conducted under a physician's supervision with regularly scheduled exams; **and**
2. Treatment is expected to be long term (3 months or longer); **and**
3. The individual meets **any** of the following:
  - a. The individual is unable to attend office-based therapy due to a serious medical or physical condition (for example, confined to the home, leaving home requires special services or involves unreasonable risk); **or**
  - b. Office based therapy has failed to control the disease and it is likely that home-based therapy will be successful; **or**
  - c. The individual suffers from severe psoriasis with a history of frequent flares which require immediate treatment to control the disease.

#### **Exclusions:**

- Systemic PUVA or oral PUVA is contraindicated in children < 12 years of age.
- Treatment of vitiligo of the acral areas (fingers, palms, soles of feet)
- Laser treatment for atopic dermatitis, contact dermatitis or other eczema
- An in-home UVB light therapy device for all other conditions not mentioned above, including but not limited to vitiligo, and when the criteria above are not met.
- UVA home therapy devices are not appropriate for home therapy. UVA therapy requires the use of photosensitizers, that should only be used under controlled conditions, and under the supervision of a physician.

**CPT/HCPCS Level II Codes** *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

#### **Established codes:**

96900	96910	96912	96913	96999	E0691
E0692	E0693	E0694			

#### **Other codes (investigational, not medically necessary, etc.):**

N/A

*Note: The code(s) listed in this policy may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.*

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## Rationale

### TARGETED PHOTOTHERAPY

#### Review of Evidence

##### Systematic Reviews

A systematic review Lopes et al (2016) identified 3 studies that compared targeted phototherapy using a 308 nm excimer lamp with NB-UVB (315 patients, 352 lesions) and 3 studies that compared the excimer lamp with the excimer laser (96 patients, 412 lesions). No differences between the excimer lamp and NB-UVB were identified for the outcome of 50% or more repigmentation (relative risk [RR], 1.14; 95% confidence interval [CI], 0.88 to 1.48). For repigmentation of 75% or more, only 2 small studies were identified, and they showed a lack of precision in the estimate (RR, 1.81; 95% CI, 0.11 to 29.52). For the 3 studies that compared the excimer lamp to the excimer laser, there were no significant differences between treatments for either 50% or greater repigmentation (RR=0.97; 95% CI, 0.84 to 1.11) or 75% or greater repigmentation (RR, 0.96; 95% CI, 0.71 to 1.30). All treatments were most effective in lesions located on the face, with the worst response being lesions on the extremities. There was some evidence of an increase in adverse events such as blistering with targeted phototherapy.

Sun et al (2015) published a systematic review of randomized controlled trials that focused on treatment of vitiligo with the 308-nm excimer laser. Reviewers identified 7 RCTs (total n=390 patients) for inclusion. None of the studies were conducted in the United States; 5 were from Asia. Three trials compared the excimer laser with an excimer lamp, and 4 compared the excimer laser with NB-UVB. The 4 studies that evaluated NB-UVB are of greatest interest to us. Repigmentation rates did not differ significantly between groups treated. Results showed that the likelihood of a 50% or more repigmentation rate was significantly higher with the excimer laser than with NB-UVB (relative risk [RR], 1.39, 95% confidence interval [CI], 1.05 to 1.85). Reviewers also stated that, in qualitative analysis, neither study showed significant benefit of the excimer laser for achieving a 75% or more repigmentation rate.

##### Randomized Controlled Trials

Poolsuwan et al (2020) compared treatment of 36 paired vitiligo lesions with either targeted phototherapy (308-nm excimer light) or NB-UVB in a single-blind study of 36 patients. Treatment of lesions with targeted phototherapy led to significant reductions in the Vitiligo Area Scoring index (VASI) score and significantly improved repigmentation grade compared to treatment with NB-UVB. An older, open-label study by Nistico et al (2012) compared 3 different treatment arms in 53 patients with localized or generalized vitiligo: (1) excimer laser plus vitamin E (n=20); (2) excimer laser plus topical tacrolimus ointment 0.1% and vitamin E (n=20); and (3) vitamin E only (control group, n=13). The investigators found that patients treated with targeted phototherapy were significantly more likely to achieve a "good" or "excellent" repigmentation response (55% in group 1 and 70% in group 2) than those who received oral vitamin E alone (0%). The rate of good or excellent responses did not differ significantly between groups that received targeted phototherapy with and without topical treatment (p=0.36). This study was limited by its open-label design and the fact that the comparator group, oral vitamin E, does not reflect optimal standard care for treatment of vitiligo.

**Table 1. Summary of Key Randomized Controlled Trial Characteristics Assessing Targeted Phototherapy for Vitiligo**

Study (Year)	Countries	Sites	Dates	Participants	Interventions
Poolsuwan et al (2020) <sup>5</sup>	Thailand	Single-center	NR	Patients 18 to 65 years of age with vitiligo with stable, symmetrically paired lesions who have not had topical therapy for ≥2 weeks or phototherapy or systemic immunosuppressive drugs for ≥8 weeks	<ul style="list-style-type: none"> <li>Localized 308-nm excimer light<sup>a</sup></li> <li>311-nm NB-UVB<sup>a</sup></li> </ul>
Nistico et al (2012) <sup>6</sup>	Italy	Single-center	NR	Patients 13 to 56 years of age with localized or generalized vitiligo	<ul style="list-style-type: none"> <li>Targeted 308-nm excimer laser plus oral vitamin E 400 IU<sup>b</sup></li> <li>Targeted 308-nm excimer laser plus topical tacrolimus 0.1% ointment plus oral vitamin E 400 IU<sup>b</sup></li> <li>Oral vitamin E 400 IU alone<sup>b</sup></li> </ul>

IU: international units; NB-UVB: narrow-band ultraviolet B; NR: not reported

<sup>a</sup> Both interventions given for 3 non-consecutive days per week x 48 treatment sessions

<sup>b</sup> Frequency of interventions were as follows: Targeted 308-nm excimer laser, twice weekly; oral vitamin E, twice daily; tacrolimus ointment, once daily. All interventions given for 12 weeks.

**Table 2. Summary of Key Randomized Controlled Trial Results Assessing Targeted Phototherapy for Vitiligo**

Study	Reduction in VASI score, mean	Repigmentation
<b>Poolsuwan et al (2020)</b>		
• N	36	36
• 308-nm excimer light	0.55 ± 0.39%	2.36 ± 1.15a
• NB-UVB	0.43 ± 0.39%	1.94 ± 1.19a
• p-value	<0.001	<0.001
<b>Nistico et al (2012)</b>		
• N	NA	53
• Phototherapy + vitamin E	NA	Good: 6/20 (30%) <sup>b,c</sup> Excellent: 5/20 (25%) <sup>b,c</sup>
• Phototherapy + tacrolimus + vitamin E	NA	Good: 8/20 (40%) <sup>b,c</sup> Excellent: 6/20 (30%) <sup>b,c</sup>
• Vitamin E alone	NA	Good: 0/13 (0%) <sup>b,c</sup> Excellent: 0/13 (0%) <sup>b,c</sup>
• p-value	NA	<0.001d

NA: not applicable; NB-UVB: narrow-band ultraviolet B; NR: not reported; VASI: Vitiligo Area Scoring index

<sup>a</sup> Repigmentation was reported as a graded score from 1 to 4 with 1 being "poor" and 4 being "excellent"

<sup>b</sup> Good repigmentation defined as 51 to 75% repigmentation; excellent repigmentation defined as 76 to 100% repigmentation

<sup>c</sup> Repigmentation reported as number of patients out of the total number of patients in subgroup (%) for each category.

<sup>d</sup> P-value reported for good to excellent repigmentation response in each intervention group versus control (vitamin E alone).

**Table 3. Study Relevance Limitations**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-up <sup>e</sup>
Poolsuwam et al (2020) <sup>5</sup> .				5,6. Differences in VASI score and repigmentation do not appear to be clinically significant; clinical significance not defined by investigators	
Nistico et al (2012) <sup>6</sup> .			2. Phototherapy groups compared to oral vitamin E, which is not optimal standard of care for vitiligo	5. Clinically significant difference in response was not prespecified	

VASI: Vitiligo Area Scoring index

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

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context for treatment is unclear; 3. Study population is unclear; 4. Study population not representative of intended use. 5. Study population is subpopulation of intended use

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator.

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

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Not CONSORT reporting of harms; 4. Not established and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefits; 2. Not sufficient duration for harms.

**Table 4. Study Design and Conduct Limitations**

Study	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Follow-up <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
Poolsuwam et al (2020) <sup>5</sup> .		1. Single-blinded to investigators only			1. Power calculations not reported	
Nistico et al (2012) <sup>6</sup> .	2. Described as an "open" study- does not appear that allocation concealment occurred	1,2. Described as an "open" study- does not appear that blinding occurred			1. Power calculations not reported	

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

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Follow-up 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).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference. f. Statistical key: 1. Test is not appropriate for outcome type: a) continuous; b) binary; c) time to event; 2. Test is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p-values not reported; 4. Comparative treatment effects not calculated.

## Retrospective Studies

Fa et al (2017) retrospectively analyzed 979 Chinese patients (3478 lesions) treated with the 308-nm targeted laser for vitiligo. Patients had Fitzpatrick skin phototype III or IV and were followed for 2 years after the last treatment. Repigmentation was assessed by 2 dermatologists. A total of 1374 (39%) lesions reached at least 51% repigmentation, with 1167 of the lesions reaching over 75% repigmentation. Complete repigmentation was seen in 219



lesions. Among the cured lesions, the recurrence rate was 44%. Patients with longer disease duration and older age experienced significantly lower efficacy rates. Application of 16 to 20 treatments resulted in higher repigmentation rates than fewer treatments and increasing the number of treatments beyond 21 did not appear to improve repigmentation rates. There was no discussion of adverse events.

In another retrospective analysis, Dong et al (2017) evaluated the use of a medium-band (304-312 nm) targeted laser for treating pediatric patients (age  $\leq 16$  years) with vitiligo. Twenty-seven patients (95 lesions) were evaluated by 2 dermatologists following a mean of 20 treatments (range, 10-50 treatments). After 10 treatment sessions, 37% of the lesions reached 50% or more repigmentation. After 20 treatment sessions, 54% of the lesions achieved 50% or more repigmentation. Six children experienced adverse events such as asymptomatic erythema, pruritus, and xerosis, all resolving in a few days.

Alhawaish et al (2013) performed a meta-analysis of the relevant literature pertaining to vitiligo and excimer laser published between 1990 and 2012. Included in the review were all relevant articles about 308-nm excimer laser and light sources assessing their efficacy in the management of vitiligo, as well as their side effects. The value of combination treatment methods was also analyzed. The available studies provide strong evidence that the excimer laser represents the most effective approach to treat vitiligo compared to ordinary phototherapy. It was noted that excimer laser is relatively safe and effective for localized disease. UV-sensitive areas respond best as well as a short duration of the disease. More frequent treatments achieve better results. Compared to other treatment modalities, the excimer laser most likely constitutes the treatment of choice for localized vitiligo. Its efficacy can be further improved in combination with other therapies such as corticosteroids, pimecrolimus, or tacrolimus.

The Italian research group also published a similar 12-week study in 2009 in which topical 4% khellin ointment was used instead of tacrolimus ointment. This study included 48 patients (16 per group), of which 45 (94%) completed treatment. The proportion of patients with a good or excellent response (see previous definitions) was 14 of 16 (88%) in the excimer laser plus vitamin E group, 14 of 16 (88%) in the excimer laser plus khellin plus vitamin E group, and 1 of 16 (6%) in the vitamin E only (control) group. The clinical response rates in the two groups receiving laser treatment were significantly higher than in the control group.

Cassaci et al (2007) sought to compare the effectiveness of NB-UVB phototherapy and 308-nm monochromatic excimer light (MEL). The study was done in a randomized, investigator-blinded and half-side comparison design. Twenty-one subjects with symmetrical vitiligo lesions were enrolled in this study. Vitiligo lesions on one body side were treated twice weekly for six months with 308-nm MEL, while NB-UVB phototherapy was used to treat lesions on the opposite side. At the end of the study, six lesions (37.5%) treated with 308-nm MEL and only one lesion (6%) treated with NB-UVB achieved an excellent repigmentation (score 4) while four lesions (25%) treated with 308-nm MEL and five lesions (31%) treated with NB-UVB showed a good repigmentation (score 3). The investigator concluded that 308-nm MEL is more effective than NB-UVB in treating vitiligo lesions and it induces repigmentation more rapidly.

Hadi et al (2004) reported on the effectiveness of excimer laser for the treatment of vitiligo. A retrospective chart review of thirty-two patients with 55 spots of vitiligo were enrolled; a population-based sample was studied that included men and women, adults and children, with different ethnic backgrounds. The treatment was started with the lowest dose, 100 mJ/cm<sup>2</sup> (comparable to one minimal erythema dose value and one multiplier). Depending on Fitzpatrick skin type, the dose was raised gradually in a stepwise fashion. In skin types I to II, the same dose was repeated twice before going up to avoid burns. Patients were treated for 30 sessions, or 75% repigmentation, whichever occurred first. Overall, 55 spots were treated: 29 (52.8%) had 75% pigmentation or greater, and 35 (63.7%) had 50% pigmentation or greater. The best results were on the face: of the 21 spots treated 15 (71.5%) had 75% pigmentation, and 16 (76.2%) had 50% pigmentation or greater. Other areas (neck, extremities, trunk, and genitals) had moderate response in comparison to the face. The least response was on the hands and feet; of the 5 spots treated only 20% showed 50% pigmentation or more. The researchers concluded that “slightly more than 50% of the patients tested showed 75% or more pigmentation of their lesions, after 30 treatments or less; most of the responders had Fitzpatrick skin type III and above. All the untreated patches (controls) remained unchanged. This demonstrates that the 308-nm excimer laser is an effective method of treatment for vitiligo.”

### **Section Summary: Targeted Phototherapy**

Published studies evaluating targeted excimer laser phototherapy for vitiligo include systematic reviews of RCTs, individual RCTs, and retrospective studies. Positive findings have been demonstrated. Randomized controlled trials have shown targeted phototherapy to be associated with statistically significant improvements in VASI scores and/or repigmentation compared to alternate treatment options. Excimer laser phototherapy increased the level of repigmentation in a greater percentage of patients over a shorter duration compared with standard therapy.

## **HOME ULTRAVIOLET B (UVB) LIGHT THERAPY**

### **Atopic dermatitis (AD)**

The initial treatment of AD typically consists of topical and non-pharmacological therapies as well as modifications in individual environments or occupations. Phototherapy is limited to those whose symptoms are not adequately controlled by the initial treatment modalities. There are numerous treatment protocols, but in general, individuals are dosed according to their minimal erythema dose and/or Fitzpatrick skin type. The AAD (2014) notes “Phototherapy can be administered on a scheduled but intermittent basis over time, or more continuously as maintenance therapy, for patients with refractory or chronic disease.”

### **Cutaneous T-cell lymphoma (CTCL)**

Non-Hodgkin lymphoma (NHL) includes two types of cutaneous lymphomas, T-cell lymphomas (CTCLs) and B-cell lymphomas (CBCLs), with CTCLs accounting for the majority of cutaneous lymphomas. According to the National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines (CPGs) in Oncology® for Primary Cutaneous Lymphomas, Mycosis Fungoides (MF) accounts for 50% to 70% of CTCL cases and Sézary syndrome (SS) accounts for less than 5% of CTCL cases. MF is considered an indolent malignancy and generally is associated with a slow progression while the median survival of SS is only 32 months from diagnosis (Trautinger, 2006). While CTCLs develop in the skin, the disease can progress and involve other areas such as lymph nodes, blood or visceral organs. Prognosis

and treatment are dependent upon a number of factors including, but not limited to extent and type of skin involvement, overall stage, whether extracutaneous disease is present and peripheral blood involvement (NCCN, 2020).

### **Mycosis Fungoides and Sézary Syndrome**

Ultraviolet light therapy is an established treatment of MF and therapies have included UVB (broad-band and narrow-band) and UVA treatments (Hodak, 2015). Phototherapy can be used at various stages of MF, either alone or in combination with systemic therapy (Hodak, 2015). The 2020 NCCN CPGs for Primary Cutaneous Lymphomas include a 2A indication for UVB therapy for patch/thin plaques in MF/SS with limited/localized or generalized skin involvement. In addition, NCCN includes a 2A indication for UVB in stage III MF/SS, noting that while generalized skin directed therapies may not be well tolerated in this population, phototherapy can be used successfully.

Due to the low incidence of MF, there is a dearth of appropriately powered RCTs, and most recommendations are generally based upon small studies, case series or expert opinion. Olsen et al reported on the results of 3 studies which included home broad-based UVB therapy which consisted of a total of 109 individuals who presented with stage 1A or 1B MF. Home treatments included daily phototherapy while office-based treatments were carried out 3 times per week. A total of 58 individuals received home-based therapy, with 48 of these 58 individuals receiving only home-based therapy and the remaining 10 individuals receiving home therapy after office-based therapy. The authors noted that maintenance regimens within the studies varied and likely affected response duration. Relapse was uncommon while individuals were on maintenance phototherapy (2/18) but was more common once maintenance phototherapy was discontinued (12/23). The authors found that individuals using home-based phototherapy were much more likely to continue maintenance phototherapy than individuals who received office-based phototherapy.

### **Pityriasis lichenoides**

UVB has also been recommended as a treatment for several other conditions. Pityriasis lichenoides is a rare collection of skin disorders that have been reported to progress to cutaneous lymphoma or an ulceronecrotic presentation, both of which carry a significant risk of mortality. Treatment is difficult and aggressive approaches are usually recommended. According to one source, the use of UVB phototherapy has been the most successful treatment method and is considered first-line therapy (Khachemoune, 2007).

### **Pruritus of hepatic or renal disease**

Pruritus of hepatic disease and renal failure are difficult to treat. Management is primarily focused on the treatment of the underlying symptoms such as pain and itching. Several treatment options are currently used, and UVB phototherapy has become widely accepted as an important tool in the management of these conditions (Wang, 2010).

### **Psoriasis**

Koek et al (2009) conducted the first randomized controlled single-blind trial comparing office-based UVB treatment with home therapy for individuals with plaque or guttate psoriasis. This study involved 196 subjects who were evaluated through the initial therapy, with the first 105 subjects followed for an additional 12 months post-treatment. The authors reported that both treatments provided significant improvement from baseline, with home therapy being non-inferior to office-based treatment as measured by the psoriasis area and severity index (PASI) and the self-administered psoriasis area and severity index (SAPASI). No significant

differences between groups were reported with regard to total cumulative radiation dose or short-term side effects.

### **Vitiligo**

Shan et al (2014) published early results of UVB home phototherapy for vitiligo in a prospective uncontrolled trial (n=93). Treatments were administered 3 times each week at variable dosages. Follow-up was conducted every 3 months up to 1 year to evaluate repigmentation and any complications. At 1 year of follow-up, 35 subjects (38%) achieved excellent repigmentation, 16 (17%) achieved good repigmentation, 15 (16%) showed moderate repigmentation, 16 (17%) had poor repigmentation, and 11 (12%) had no repigmentation. A total of 25 (27%) individuals discontinued treatment due to poor repigmentation. This study was hampered by several design limitations, including a lack of randomization, and lack of appropriate comparator groups.

Eleftheriadou (2014) conducted a pilot trial to determine the feasibility of conducting a multicenter randomized controlled trial (RCT) to assess the safety and effectiveness of home hand-held NB-UVB phototherapy compared with topical treatments for repigmentation of vitiligo. Results showed that a larger RCT evaluating home hand-held phototherapy is feasible and acceptable to participants and healthcare providers. This trial was not intended as an efficacy trial.

A prospective cohort trial enrolled 94 individuals with non-segmental vitiligo to evaluate the efficacy and safety of home and outpatient narrowband UVB therapy. Over a period of 6 months, 48 participants received treatment at home while 46 received outpatient treatment. Primary outcomes included efficacy, quality of life and adverse events. Overall, results were similar at 6 months between groups with higher efficacy seen on some measures for the outpatient group (Zhang, 2019). Further investigation of the efficacy and safety of NB-UVB as a home-treatment for non-segmental vitiligo, in the setting of a randomized trial, is warranted.

Liu et al (2020) published the results of a randomized pilot trial to determine the efficacy and safety of narrowband UVB phototherapy at home compared to hospital management of limited new-onset vitiligo. A total of 100 individuals with new-onset vitiligo (< 3 months) and < 5% body surface area involvement were randomized to either a home-based or a hospital-based treatment group and administered UVB phototherapy 3 times a week. At study-end (8 weeks), home- and hospital-based treatment showed similar efficacy but the frequency of adverse events, such as painful erythema, burning, blistering, and excessive hyperpigmentation, were increased in the home-based.

The current evidence does not support the safety and efficacy of home-based UVB phototherapy devices compared with in-office or alternative treatments for vitiligo. The published literature does not show that use of a home-based UVB phototherapy device provides additional benefits to the individual user.

### **Summary: UVA home therapy devices**

The use of UVA as a home therapy has not been shown to be safe and effective when compared to the other alternatives, such as office or facility-based treatment UVA therapy or UVB therapy. The American Academy of Dermatology (AAD) 2014 notes that given the limited number of head-to-head trials, there is no definitive recommendation regarding which form of phototherapy is more effective. UVA therapy requires the concurrent use of photosensitizers, which greatly increase the risk of complications. UVB therapy does not involve the use of photosensitizers.

## PSORALENS WITH ULTRAVIOLET A

### Systemic Reviews

Bae et al (2017) published a systematic review and meta-analysis on the use of phototherapy for the treatment of vitiligo. The literature search, conducted through January 2016, identified 35 unique studies for inclusion with 1201 patients receiving NB-UVB and 227 patients receiving PUVA. The category of evidence and strength of recommendation were based on study design of the selected studies. The outcome of interest was the repigmentation rate. Meta-analytic results are summarized in Table 5. Adverse events were not discussed.

**Table 5. Response Rates to NB-UVB and PUVA in the Treatment of Vitiligo by Treatment Duration**

Treatment	Duration, mo.	≥50% Repigmentation (95% CI), %	≥75% Repigmentation (95% CI), %
NB-UVB	6	37.4 (27.1 to 47.8)	19.2 (11.4 to 27.0)
NB-UVB	12	56.8 (40.9 to 72.6)	35.7 (21.5 to 49.9)
PUVA	6	23.5 (9.5 to 37.4)	8.5 (0 to 18.3)
PUVA	12	34.3 (23.4 to 45.2)	13.6 (4.2 to 22.9)

Adapted from Bae et al (2017).<sup>9</sup>

CI: confidence interval; NB-UVB: narrowband ultraviolet B; PUVA: psoralens with ultraviolet A.

### Randomized Controlled Trials

Bansal et al (2013) evaluated the efficacy of psoralen-NB-UVB (P-NB-UVB) vs. NB-UVB in vitiligo in a randomized study. Forty-five Indian patients (over age 13 years) with vitiligo involving more than 5% body surface area were randomly assigned to receive either NB-UVB or P-NB-UVB treatment. Both groups received NB-UVB exposure 3 times weekly, with a total of 60 sessions. The extent of repigmentation achieved was calculated on the basis of Vitiligo Area Severity Index (VASI) scoring. Forty patients were available for analysis at the end of the study. The extent of repigmentation in the P-NB-UVB group was statistically significantly greater in face and neck ( $P=.006$ , t-test) and hands ( $P=.007$ , t-test) in comparison with the NB-UVB group (t-test). Percentage reduction in VASI scores was statistically significantly greater in the P-NB-UVB group (29.2% vs. 21.7%,  $P=.043$ , t-test). The response to P-NB-UVB therapy started earlier than the response to NB-UVB. After excluding sunlight as a confounding factor, treatment response was also significantly better in the P-NB-UVB group ( $P=.005$ ). Investigators concluded addition of psoralen increased the extent of repigmentation due to NB-UVB therapy in vitiligo.

Sapam et al (2012) compared the efficacy and adverse effects of NB-UVB with oral psoralen PUVA therapy in the treatment of vitiligo in a parallel-group, assessor blinded, randomized, controlled trial. Patients aged 13-70 years with vitiliginous lesions involving more than 5% body surface area were eligible for the study. In total, 56 patients were randomized in a 1:1 ratio to oral PUVA or NB-UVB phototherapy groups. Patients were assessed for the percentage of repigmentation over the depigmented areas as the primary outcome measure at each visit during the first 3 months and then monthly within the next 3 months. The incidence of adverse effects was also noted during the study period as the secondary outcome measure. The median repigmentation achieved at the end of the 6-month therapy course was 45% in the NB-UVB group and 40% in the oral PUVA group. Focal vitiligo had the best response in both treatment groups. There were lesser adverse effects within the NB-UVB (7.4%) than in the PUVA (57.2%) group. Two PUVA patients discontinued therapy due to severe dizziness. There was no significant difference in the mean degree of repigmentation; however, NB-UVB carried a greater response rate and might be superior to oral PUVA with better tolerance and color

match with the surrounding normal skin, as well as fewer side effects in the treatment of vitiligo.

Bhatnagar et al (2007) evaluated the efficacy of NB-UVB compared to trimethylpsoralen PUVA. In this randomized, open, prospective study, 50 patients were divided equally in PUVA and NB-UVB groups. The mean degree of repigmentation attained in the NB-UVB group was 52.24% over a mean treatment period of 6.3 months, whereas in the PUVA group it was 44.7% in a mean period of 5.6 months ( $P=0.144$ ). After excluding the results of therapy-resistant sites, that is, hands and feet, the mean degree of repigmentation in the NB-UVB group was 67.57%, whereas in the PUVA group it was 54.2% ( $P=0.007$ ). The researchers concluded that NB-UVB performed better in comparison to TMP PUVA in terms of mean total repigmentation when traditionally considered therapy-resistant sites were excluded.

Yones et al (2007) published an RCT that used a psoralen formulation available in the United States. The trial enrolled 56 patients in the United Kingdom who had non-segmental vitiligo. Outcome assessment was blinded. Patients were randomized to twice-weekly treatments with methoxsalen hard gelatin capsules (8-MOP) psoralen plus UVA ( $n=28$ ) or NB-UVB therapy ( $n=28$ ). The NB-UVB treatments were administered in a Waldmann UV500 cabinet containing 24 Phillips 100 NB-UVB fluorescent tubes. In the PUVA group, the starting dose of irradiation was  $0.5 \text{ J/cm}^2$ , followed by  $0.25 \text{ J/cm}^2$  incremental increases if tolerated. Patients were evaluated after every 16 sessions and followed for up to 1 year. All patients were included in the analysis. The median number of treatments received was 49 in the PUVA group and 97 in the NB-UVB group. At the end of treatment, 16 (64%) of 25 patients in the NB-UVB group had greater than 50% improvement in body surface area affected compared with 9 (36%) of 25 patients in the PUVA group. In addition, 8 (32%) of 25 in the NB-UVB group and 5 (20%) of 25 patients PUVA group had at least 75% improvement in the body surface area affected. Although authors did not provide p values in their outcome table. They stated that the difference in improvement did not differ significantly between groups for the patient population as a whole. Among patients who received at least 48 treatments, improvement was significantly greater in the NB-UVB group ( $p=0.007$ ). A total of 24 (96%) patients in the PUVA group and 17 (68%) in the NB-UVB group developed erythema at some point during treatment; this difference was statistically significant ( $p=0.02$ ).

### **Section Summary: Psoralens With Ultraviolet A**

There is evidence from multiple studies that PUVA and NB-UVB are effective for treating vitiligo when first-line therapies have failed. Studies comparing PUVA with NB-UVB have had mixed findings. Meta-analyses have shown that patients receiving NB-UVB experienced higher rates of repigmentation than patients receiving PUVA, though the differences were not statistically significant. Patients treated with PUVA experienced higher rates of adverse events such as nausea and erythema. Analyses of treatment duration found that repigmentation rates following 12 months of treatment were higher compared with rates following 6 months of treatment.

### **LIGHT THERAPY FOR CHILDREN WITH VITILIGO**

Kanwar et al (2012) presented a brief update regarding the various safe therapeutic modalities for vitiligo, for use in children. Vitiligo usually presents in childhood and young adulthood. Approximately one half to one third of cases occurs by 20 years of age, and about 25% develop before eight years, with a mean age of onset between four and five years. Topical steroids are often the first line of treatment because they are an easy and convenient mode of

treatment. If the body surface area (BSA) involved in the child is < 20%, and the disease is not rapidly spreading, then topical therapy is first choice. The only drawback of long-term topical steroid usage is its side effects. Topical calcineurin inhibitors are proving to provide results similar to topical steroid, but their drawback is, it is costly and not recommended for children below two years of age. Results of treatment outcome have been reported to be moderately successful, particularly in patients with localized vitiligo. Narrow band UVB has proven to be effective in vitiligo. Much data of NB-UVB exists in adults. Due to fear of long-term toxicity (because of patients prolonged life expectancy after treatment) there is limited data on treatment in children. In children with vitiligo affecting  $\geq 20\%$  of body surface area, NB-UVB has shown to be a safe option. Studies have shown positive effects of NB-UVB in children with vitiligo, but there is insufficient data to provide recommendation for the safe maximum dose and duration of therapy of NB-UVB in children.

There is an overall consistency in the clinical literature that systemic PUVA or oral PUVA is contraindicated in children younger than 12 years of age; it is restricted to children of > 12 years and those who have widespread vitiligo (i.e.,  $\geq 20\%$  BSA); however, topical PUVA can be safely used in children of two years and more who have up to 20% of their body affected.

Ezzedine et al (2016) discussed management strategies for vitiligo in the pediatric population. Authors concluded that a variety of phototherapy modalities exist that have been shown to be beneficial in pediatric vitiligo. Generalized phototherapy is often performed in extensive disease and in disease that is spreading rapidly. Psoralens and UVA (PUVA) has been historically used in vitiligo with good benefit, but there is difficulty with nausea, compliance of eyewear, office visits, and many side effects including phototoxic reactions. Therefore, PUVA has been largely replaced by narrowband UVB (NB UVB). Furthermore, in head-to-head study, there has been demonstrable increased repigmentation that was not significant over PUVA. In children, NB UVB has become the therapy of choice and can produce two types of benefits: (1) repigmentation, and (2) stabilization, the latter being an important way to gain control over widespread disease. Some benefit can be achieved with the addition of topical corticosteroids. Other forms of phototherapy that have been described as safe and effective for long-term therapy of pediatric vitiligo include excimer laser, targeted UVB, and targeted UVA. Side effects of phototherapy include itch, burning, erythema, stinging, blistering, and phototoxicity. Targeted phototherapy may not allow for disease stabilization in extensive disease but does limit side effects to the local site treated. Excimer laser is most beneficial in segmental vitiligo when performed early on in disease. Phototherapy is often more effective in darker patients and the benefits of phototherapy in Fitzpatrick type I skin (lightest skin type) do not outweigh the risk. Although long-term follow-up of pediatric patients with vitiligo who received phototherapy has not been conducted, the risk of carcinogenesis after phototherapy probably persists lifelong, requiring on-going full body skin examinations for screening after therapy. As some patients with vitiligo will have circulating ANAs, which could sensitize them, screening for ANAs before systemic phototherapy can be helpful.

Phiske et al (2016) indicate that treatment modalities for vitiligo in children do not differ from those used in adults, but some are age specific. Some treatment modalities with potential serious side effects may not be justified in children. If the body surface area (BSA) involved in the child is < 20%, and the disease is not rapidly spreading, then topical therapy (steroids and topical calcineurin inhibitors) is first choice for lesions over face, neck, and genital areas. Excellent repigmentation rates have been reported with topical steroids, whereas calcineurin inhibitors have comparable efficacy and a better safety profile compared with topical steroids.

PUVA oral psoralen plus UVA is contraindicated in children < 12 years of age (due to long term serious side effects), it is restricted to children of > 12 years and those who have widespread vitiligo (i.e.,  $\geq 20\%$  BSA). Topical psoralen plus UVA is a safer treatment modality for children with limited vitiligo, children younger than two years of age and who have up to 20% of their body affected. It proves to be effective if administered carefully, as there is no necessity to take precautions for ocular toxicity or for hepatic dysfunction which is needed for oral PUVA. It gives favorable response in segmental vitiligo. If the BSA involved is > 20%, phototherapy should be considered. NB UVB has better overall repigmentation rates and safety profile. A meta-analysis found that NB UVB was the most effective and safest therapy for generalized vitiligo. Long - term NB UVB therapy may carry less risk for skin cancer than PUVA therapy. In children, if no response is observed after six months, further therapy should be discontinued.

Cho et al (2011) retrospectively evaluated the efficacy and safety of 308-nm excimer laser treatment in 30 childhood vitiligo patients. Forty childhood vitiligo lesions were studied, and half of them showed 50% repigmentation and 12.5% had greater than 75% repigmentation. Vitiligo lesions over sun-exposed areas responded better. Side-effects reported with this laser are perilesional hyperpigmentation, burns, and folliculitis.

Hui-Lan et al (2009) investigated 49 pediatric patients in a single-blinded, randomized study comparing 308-nm excimer laser therapy together with topical 1% pimecrolimus cream twice daily (group A) with excimer laser therapy twice per week (group B). Of 48 patients evaluated after 30 weeks of treatment, 71% of patients from group A achieved grade III or IV repigmentation compared with 50% in group B. A significant difference was found between group A and B at the end of 30 weeks of treatment.

Al Otaibi et al (2009) conducted a controlled prospective trial in 34 patients with localized vitiligo (age 3-21 years), treatment was given twice-weekly for a period of 13 weeks with a spot size 15- and 25-mm. Half of the children had at least 50% repigmentation, facial lesions responded better in comparison to other sites.

### **Section Summary: Light Therapy For Children With Vitiligo**

The available literature suggests that phototherapy may be considered in children when more than 20% of their body surface is involved. NB-UVB is safer than PUVA and should therefore be the treatment of choice when other conservative measures have failed. Combinations of topical therapy and NB-UVB have shown good results and can be tried in patients who fail to show a good response with NB-UVB alone. It remains unknown how many treatments and what frequencies would increase the risk of developing a treatment-related skin cancer. Children with vitiligo that is limited to focal lesions who do not respond to topical therapy have been shown to benefit from excimer laser phototherapy. Published studies reveal that NB-UVB and excimer laser therapy have been successfully performed in children as young as 3 years of age.

### **DERMATITIS AND EXCIMER LASER**

The excimer laser system is a hand-held UVB laser light source, which utilizes a xenon chloride gas mixture and emits intense, targeted UVB at a monochromatic wavelength of 308 nm. Compared with traditional UVB therapy, it provides an advantage in that a greater intensity of UVB radiation can be used to target lesions while sparing unaffected areas.



Mehraban (2014) published a systemic review summarizing all the experiments, clinical trials and case reports on 308 nm excimer laser in dermatological disorders. 308-nm excimer laser has currently a verified efficacy in treating skin conditions such as vitiligo, psoriasis, atopic dermatitis, alopecia areata, allergic rhinitis, folliculitis, granuloma annulare, lichen planus, mycosis fungoides, palmoplantar pustulosis, pityriasis alba, CD30+ lymphoproliferative disorder, leukoderma, prurigo nodularis, localized scleroderma and genital lichen sclerosis. Further large-scale studies were recommended in order to fully affirm the safety profile of the 308 nm laser considering the potential risk of malignancy.

Beggs (2015) conducted an extensive literature search to find articles pertaining to dermatologic conditions treated with the 308 nm excimer laser. The outcomes and results were compiled into different dermatologic conditions treated with the excimer laser. The 308 nm excimer laser proved to have a wide range of uses for focal inflammatory and hypopigmented conditions. The authors concluded that larger studies and studies evaluating the long-term effects of the excimer laser are needed.

### **Section Summary: Dermatitis And Excimer Laser**

Due to the small sample sizes, lack of ongoing current literature and the few published studies demonstrating the use of excimer laser for atopic dermatitis, efficacy and safety have not been documented. The use of all UV treatments contains a risk for development of skin cancer. With the greater intensity of UVB radiation used by the 308 nm excimer laser, the risk in comparison to standard therapy is unknown. Evidence to support excimer laser therapy for the treatment of atopic dermatitis is lacking, further studies are needed.

### **Summary of Evidence**

Light therapy for skin conditions include PUVA, NB-UVB, and targeted excimer laser phototherapy. Overall, studies to date support the safety and efficacy of these light therapies for vitiligo, in both pediatric and adult populations. In most instances where vitiligo is recalcitrant to first-line therapies, NB-UVB and targeted excimer laser, with or without topical medications, have emerged as preferred second-line treatments. The percentage of body surface area affected, age of the patient and the area of treatment should all be considered when determining the best modality for treatment of childhood vitiligo.

Phototherapy and photochemotherapy (i.e., UVA, UVB and PUVA) may be prescribed for adults when severe cases of atopic dermatitis, contact dermatitis and other eczema have failed to respond to immunosuppressants. Evidence to support efficacy and safety of excimer laser therapy for the treatment of atopic or contact dermatitis and other eczema is lacking.

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## **Supplemental Information**

### **PRACTICE GUIDELINES AND POSITION STATEMENTS**

#### **American Academy of Dermatology**

The American Academy of Dermatology (AAD) website provides information on vitiligo treatments and includes PUVA and excimer laser as options. There are no practice guidelines or protocols for the use of UVB for vitiligo patients. The AAD also provides patient information on vitiligo treatment and mentions NB-UVB as a treatment option.

The AAD (2014) indicates that the successful use of UV light for atopic dermatitis (AD) has led to the investigation of laser light technology as another possible treatment. Various laser modalities, including excimer, diode, and pulsed dye lasers, have been tested in AD patients, with some improvement in symptoms such as pruritus and quality of life (QOL). Given a very limited number and quality of reports, lasers are not recommended for the treatment of AD at this time.

### **British Association of Dermatologists**

The British Association of Dermatologists (2008) reviewed and updated in (2021) guidelines on the diagnosis and management of vitiligo were published by a collaboration of several U.K. organizations, including the British Association of Dermatologists, the Royal College of Physicians of London, and the Cochrane Skin Group. The guidelines included the following statements:

#### **Light and laser monotherapy and combination therapies**

R20 Offer NB-UVB (whole body or localized, e.g. home based handheld) as first-line phototherapy to people with vitiligo who have an inadequate response to topical therapy and/or who have extensive or progressive disease. As a prolonged course is generally required, discuss the risk-benefit ratio, particularly for children .<sup>§</sup> This may be combined with topical calcineurin inhibitor† (more evidence for tacrolimus) or potent topical corticosteroid, for localized sites. Counsel patients on the significant risk of loss of response upon treatment cessation.

[§There is lack of data on the skin cancer risk for high cumulative exposures in children with less deeply pigmented skin (Fitzpatrick skin types I–III), hence the risk-benefit ratio needs to be carefully considered. Prior to combination NB-UVB and topical tacrolimus treatment, advise patients that there is a theoretical increased risk of skin cancer with this combination of treatment. A shared decision should be made with the person with vitiligo, taking into account other alternatives, the individual's personal and family history of skin cancer risk and the impact of the vitiligo. The evidence for potent topical corticosteroid is limited. Prior to this combination, consider the risk–benefit ratio of the prolonged use of potent topical corticosteroid.]

R21 Inform people with vitiligo who are eligible for NB-UVB therapy of the requirements (depending on local protocols: a pretherapy assessment, medical photographs taken prior to and during follow-ups at 3–6 months, two to three sessions weekly possibly for up to 1 year), and the likely response depending on the affected anatomical site (e.g. the face and trunk usually achieve better repigmentation than acral sites). Alternatively, body surface area (BSA) and areas affected by vitiligo should be documented, or patients could use personal devices to take photographs if medical photography is not available or not practical.

R22 Only consider PUVA or PUVAsoL in adults with vitiligo if treatment with NB-UVB is unavailable or has been ineffective.

R23 Consider excimer laser or light in people with localized vitiligo in combination with topical calcineurin inhibitors (more evidence for tacrolimus). Prior to treatment, advise patients that there is a theoretical increased risk of skin cancer with this combination of treatment. This treatment is not widely available on the NHS, but is available in a limited number of centres with a specialist interest.

R24 Consider CO2 laser in combination with 5-fluorouracil in adults with nonsegmental vitiligo on the hands and feet if other treatments have been ineffective (apply 5-fluorouracil once daily for 7 days per month for 5 months; CO2 laser treatments once a month for 5 months). This treatment is not widely available on the NHS, but can be accessed in a limited number of centres with a specialist interest.

There is insufficient evidence to recommend combination treatment of potent or very potent topical steroid with NB-UVB plus CO2 laser for people with vitiligo.

### **European Dermatology Forum**

The European Dermatology Forum (2013) published consensus guidelines on the management of vitiligo. The guidelines stated that oral psoralens with ultraviolet A are commonly used in adults with generalized vitiligo as second-line treatment. The guidelines also stated that targeted phototherapy is indicated for localized vitiligo, particularly small lesions of recent onset and childhood vitiligo, to avoid adverse effects due to total body irradiation and when total body irradiation is contraindicated. The guidelines were based on expert opinion.

### **European Task Force on Atopic Dermatitis/EADV Eczema Task Force**

In 2020, the ETFAD/EADV Eczema Task Force updated its position paper to indicate that beside natural sunlight, phototherapy for atopic dermatitis (AD) may be useful with different artificial light sources: broad-spectrum UVB (280–315 nm), narrowband UVB (311–313 nm), broadband UVA (UVA) (315–400 nm), UVA1 (340–400 nm), UVA1 cold light (with seawater baths) plus UVB (balneophototherapy) and psoralen plus UVA. UVA1 phototherapy can be applied as moderate-dose (50 J/cm<sup>2</sup>) and low-dose (10 J/cm<sup>2</sup>) regimen, whereas high dose (130 J/cm<sup>2</sup>) is not recommended anymore for AD treatment. Using 308-nm monochromatic excimer light allows the treatment of only limited areas. Though blue light has been used for AD in an uncontrolled trial, treatment with longer wavelengths has not been carefully studied for AD and is therefore not recommended.

### **Vitiligo Task Force**

The international Vitiligo Task Force published a 2023 consensus statement on the management of vitiligo. First-line recommendations include topical corticosteroids or immunomodulators. The task force does not recommend oral psoralen plus ultraviolet A (PUVA), but recommends topical PUVA as an option for localized lesions. The statement includes recommendations for the use of excimer devices in patients with localized disease.

### **Vitiligo Working Group**

The Vitiligo Working Group (now the Global Vitiligo Foundation) is supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, part of the National Institutes of Health. In 2017, the group published guidelines on current and emerging treatments for vitiligo. The Working Group indicated that psoralens with ultraviolet A (PUVA) has largely been replaced by narrowband ultraviolet B, but that “PUVA may be considered in patients with darker Fitzpatrick skin phototypes or those with treatment-resistant vitiligo (level I evidence).” The Working Group also stated that “Targeted phototherapy (excimer lasers and excimer lamps) can be considered when <10% of body surface area is affected (level II evidence).”

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## Government Regulations

### National:

Treatment of Psoriasis. Pub 100-3; Section 250.1. Version 1

### Indications and Limitations of Coverage

Psoriasis is a chronic skin disease, for which several conventional methods of treatment have been recognized as covered. These include topical application of steroids or other drugs; ultraviolet light (actinotherapy); and coal tar alone or in combination with ultraviolet B light (Goeckerman treatment).

A newer treatment for psoriasis uses a psoralen derivative drug in combination with ultraviolet A light, known as PUVA. PUVA therapy is covered for treatment of intractable, disabling psoriasis, but only after the psoriasis has not responded to more conventional treatment. The Medicare Administrative Contractor should document this before paying for PUVA therapy.

In addition, reimbursement for PUVA therapy should be limited to amounts paid for other types of photochemotherapy; ordinarily, payment should not be allowed for more than 30 days of treatment, unless improvement is documented.

### Local:

There is no local coverage determination (LCD).

*(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)*

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## Related Policies

N/A

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*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through April 1, 2024, the date the research was completed.*

### Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/14	8/19/14	8/22/14	Joint policy established
1/1/16	10/13/15	10/27/15	Routine maintenance
1/1/17	10/11/16	10/11/16	<ul style="list-style-type: none"> <li>• Routine maintenance</li> <li>• JUMP criteria is more specific than BCBSA policy – we address age, systemic and topic treatment and include restrictions as to area of body being treated</li> </ul>
1/1/18	10/19/17	10/19/17	<ul style="list-style-type: none"> <li>• Routine maintenance</li> </ul>
1/1/19	10/16/18	10/16/18	<ul style="list-style-type: none"> <li>• Routine maintenance</li> </ul>
1/1/20	10/15/19		<ul style="list-style-type: none"> <li>• Routine maintenance</li> <li>• Title changed from “Light therapy for vitiligo” to “Light and Laser therapy for vitiligo and atopic dermatitis”</li> <li>• Excimer laser for atopic dermatitis /eczema added – INV</li> </ul>
9/1/20	6/16/20		Routine maintenance
9/1/21	6/15/21		<p>Routine maintenance</p> <p>Added HCPCS codes E0691-E0694 to established.</p> <p>References updated – policy statement updated to include:</p> <p>Home ultraviolet B (UVB) light therapy is considered established for any one of the following diagnoses:</p> <p>Atopic dermatitis, when topical treatment alone has failed; or</p> <p>Pityriasis lichenoides; or</p> <p>Pruritus of hepatic disease; or</p> <p>Pruritus of renal failure; or</p> <p>Psoriasis, when topical treatment alone has failed; or</p> <p>Cutaneous T-cell lymphoma including mycosis fungoides and Sézary syndrome.</p>



			<p>Added inclusion/exclusion to include statement Home ultraviolet B (UVB) light therapy.</p> <p>Added section on HOME ULTRAVIOLET B (UVB) LIGHT THERAPY under rationale.</p>
9/1/22	6/21/22		Routine maintenance
9/1/23	6/13/23		<ul style="list-style-type: none"> <li>• Routine maintenance</li> <li>• Vendor: N/A (ky)</li> </ul>
9/1/24	6/11/24		<ul style="list-style-type: none"> <li>• Routine maintenance</li> <li>• Vendor: Codes E0691, E0692, E0693, and E0694 managed by Northwood. (ky)</li> </ul>

Next Review Date: 2<sup>nd</sup> Qtr, 2025

**BLUE CARE NETWORK BENEFIT COVERAGE**  
**POLICY: LIGHT AND LASER THERAPY FOR VITILIGO AND ATOPIC DERMATITIS**

**I. Coverage Determination:**

<b>Commercial HMO (includes Self-Funded groups unless otherwise specified)</b>	Covered, policy criteria apply
<b>BCNA (Medicare Advantage)</b>	Refer to the Medicare information under the Government Regulations section of this policy.
<b>BCN65 (Medicare Complementary)</b>	Coinsurance covered if primary Medicare covers the service.

**II. Administrative Guidelines:**

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.



## Medical Policy

### Phototherapy: PUVA, UV-B and Targeted Phototherapy

#### Table of Contents

- [Policy: Commercial](#)
- [Authorization Information](#)
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- [Description](#)
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#### Policy Number: 059

BCBSA Reference Number: 2.01.47; 2.01.86 (For Plans internal use only)

#### Related Policies

Dermatologic Applications of Photodynamic Therapy, #[463](#)

#### Policy

**Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue<sup>SM</sup> and Medicare PPO Blue<sup>SM</sup> Members**

#### Photochemotherapy with psoralen plus ultraviolet A (PUVA) - OFFICE SETTING

PUVA treatment for the following conditions may be considered [MEDICALLY NECESSARY](#):

- Parapsoriasis
- Atopic dermatitis/ Eczema
- Lichen planus
- Urticaria pigmentosa
- Chronic recalcitrant dermatitis
- Pruritus
- Dyshidrosis
- pityriasis lichenoides chronica
- Alopecia areata (if conservative treatment has failed)
- Vitiligo.

PUVA for the treatment of severe, disabling psoriasis, which is not responsive to other forms of conservative therapy (eg, topical corticosteroids, coal/tar preparations, and ultraviolet light), may be considered [MEDICALLY NECESSARY](#).<sup>5</sup>

PUVA treatment as initial (primary) treatment for mycosis fungoides stage I (early infiltrative) and stage II (infiltrative plaques) may be considered [MEDICALLY NECESSARY](#).

PUVA treatment is [INVESTIGATIONAL](#) for other conditions not listed above.

### **Relative Contraindications to PUVA Therapy<sup>1</sup>**

The following are relative contraindications to PUVA therapy. Coverage is determined at the physician's discretion:

- Pregnancy (absolute contraindication)
- History or presence of melanoma or other skin cancer
- History of arsenic or ionizing radiation exposure.

Certain diseases may be worsened by UV light, including:

- Lupus
- Xeroderma pigmentosum
- Albinism
- Porphyria
- Cataracts
- Aphakia
- Severe heart, kidney, or liver disease
- Certain diseases with suppressed immune systems
- Patients allergic to this form of light.

### **Ultraviolet B phototherapy (UV-B) - OFFICE SETTING**

UV-B phototherapy which may be administered in 3 different ways may be considered **MEDICALLY NECESSARY**:

- Broadband in a light box
- Narrow band in a light box
- Narrowband emitted or delivered by laser.<sup>2</sup>

UV-B phototherapy may be considered **MEDICALLY NECESSARY** for patients with the following:

- Alopecia areata (if conservative treatment has failed)
- Atopic dermatitis / Eczema
- Chronic recalcitrant dermatitis
- Lichen planus
- Mild to moderate psoriasis that is unresponsive to conservative treatment
- Moderate to severe localized psoriasis (i.e., comprising less than 20% body area) for which NB-UVB or PUVA are indicated
- Mycosis fungoides
- Parapsoriasis
- Pityriasis lichenoides chronica
- Pruritus
- Urticaria pigmentosa
- Vitiligo.\*

UV-B phototherapy may be considered **INVESTIGATIONAL** for other conditions not listed above.

**Phototherapy (including light boxes, panels, or visors)** may be considered **INVESTIGATIONAL** for the following conditions because light therapy has not been shown to be more effective than placebo for:

- Jet lag
- Disorders related to shift work or irregular work cycles
- Delayed or altered sleep phase syndromes
- Circadian rhythm disorders.

### **Targeted phototherapy - OFFICE SETTING**

\*Targeted phototherapy for the **treatment of vitiligo** may be considered **MEDICALLY NECESSARY** when the following criteria are met:<sup>3</sup>

- The area being treated cannot be adequately reached during light box therapy (eg, face, scalp, fingers/toes, neck, intertriginous areas), **or**
- There is contraindication to total body phototherapy (eg, pregnancy or a history of skin cancer).

Targeted phototherapy may be considered **MEDICALLY NECESSARY** for the **treatment of moderate to severe localized psoriasis** (ie, comprising less than 20% body area) for which NB-UVB or PUVA are indicated.<sup>4</sup>

Targeted phototherapy may be considered **MEDICALLY NECESSARY** for the **treatment of mild to moderate localized psoriasis** that is unresponsive to conservative treatment.<sup>4</sup>

Targeted phototherapy is considered **INVESTIGATIONAL** for the **first-line treatment of mild psoriasis**.<sup>4</sup>

Targeted phototherapy is considered **INVESTIGATIONAL** for the **treatment of generalized psoriasis or psoriatic arthritis**.<sup>4</sup>

### Ultraviolet B phototherapy (UV-B) - HOME SETTING

Home ultraviolet light booth for UV-B phototherapy may be considered **MEDICALLY NECESSARY** for patients with severe psoriasis.

Home Narrow Band UV-B phototherapy system (handheld units)<sup>3</sup> may be considered **MEDICALLY NECESSARY** for targeted treatment of:

- Moderate-to-severe localized psoriasis comprising less than 10% body area that is unresponsive to conservative treatment; **AND**
- Outpatient UVB phototherapy has been utilized and has demonstrated to be beneficial and is expected to be long-term.

Home Narrow Band UV-B phototherapy system (handheld units)<sup>3</sup> is considered **INVESTIGATIONAL** for:

- First-line treatment of mild psoriasis
- Treatment of generalized psoriasis or psoriatic arthritis
- All other dermatologic conditions.

Targeted phototherapy may be performed in the home setting under the supervision of a physician using FDA-approved prescription-only light sources.

**Note:** We will only cover for **either** the home UV-B booth or the home narrow band UV-B handheld unit. We will not cover both devices simultaneously.

### Prior Authorization Information

#### Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

#### Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is <b>not required</b> .
Commercial PPO and Indemnity	Prior authorization is <b>not required</b> .
Medicare HMO Blue <sup>SM</sup>	Prior authorization is <b>not required</b> .
Medicare PPO Blue <sup>SM</sup>	Prior authorization is <b>not required</b> .

## CPT Codes / HCPCS Codes / ICD Codes

*Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.*

*Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.*

*The following codes are included below for informational purposes only; this is not an all-inclusive list.*

**The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:**

### CPT Codes

CPT codes:	Code Description
96912	Photochemotherapy; psoralens, and ultraviolet A (PUVA)
96913	Photochemotherapy (Goeckerman and/or PUVA) for severe photoresponsive dermatoses requiring at least 4-8 hours of care under direct supervision of the physician (includes application of medication and dressings)

**The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT codes above if medical necessity criteria are met:**

### ICD-10 Diagnosis Codes

ICD-10CM diagnosis codes:	Code Description
C84.00	Mycosis Fungoides, Unspecified Site
C84.01	Mycosis Fungoides, Lymph Nodes of Head, Face, And Neck
C84.02	Mycosis Fungoides, Intrathoracic Lymph Nodes
C84.03	Mycosis Fungoides, Intra-Abdominal Lymph Nodes
C84.04	Mycosis Fungoides, Lymph Nodes of Axilla and Upper Limb
C84.05	Mycosis Fungoides, Lymph Nodes of Inguinal Region and Lower Limb
C84.06	Mycosis Fungoides, Intrapelvic Lymph Nodes
C84.07	Mycosis Fungoides, Spleen
C84.08	Mycosis Fungoides, Lymph Nodes of Multiple Sites
C84.09	Mycosis Fungoides, Extranodal And Solid Organ Sites
H02.731	Vitiligo of right upper eyelid and periocular area
H02.732	Vitiligo of right lower eyelid and periocular area
H02.733	Vitiligo of right eye, unspecified eyelid and periocular area
H02.734	Vitiligo of left upper eyelid and periocular area
H02.735	Vitiligo of left lower eyelid and periocular area
H02.736	Vitiligo of left eye, unspecified eyelid and periocular area
H02.739	Vitiligo of unspecified eye, unspecified eyelid and periocular area
L20.0	Besnier'S Prurigo
L20.81	Atopic Neurodermatitis
L20.82	Flexural Eczema
L20.84	Intrinsic (Allergic) Eczema
L20.89	Other Atopic Dermatitis
L25.9	Unspecified Contact Dermatitis, Unspecified Cause
L28.0	Lichen Simplex Chronicus

L28.1	Prurigo Nodularis
L28.2	Other Prurigo
L29.0	Pruritus ani
L29.1	Pruritus scroti
L29.2	Pruritus vulvae
L29.3	Anogenital pruritus, unspecified
L29.8	Other Pruritus
L29.9	Pruritus, Unspecified
L30.1	Dyshidrosis [Pompholyx]
L30.9	Dermatitis, unspecified
L41.0	Pityriasis Lichenoides Et Varioliformis Acuta
L41.1	Pityriasis Lichenoides Chronica
L41.3	Small plaque parapsoriasis
L41.4	Large plaque parapsoriasis
L41.5	Retiform parapsoriasis
L41.8	Other Parapsoriasis
L41.9	Parapsoriasis, unspecified
L43.0	Hypertrophic lichen planus
L43.1	Bullous lichen planus
L43.2	Lichenoid drug reaction
L43.3	Subacute (active) lichen planus
L43.8	Other Lichen Planus
L43.9	Lichen planus, unspecified
L63.0	Alopecia (capitis) totalis
L63.1	Alopecia universalis
L63.2	Ophiasis
L63.8	Other alopecia areata
L63.9	Alopecia areata, unspecified
L66.1	Lichen Planopilaris
L80	Vitiligo
L94.5	Poikiloderma vasculare atrophicans
L98.1	Factitial Dermatitis
Q82.2	Congenital cutaneous mastocytosis

The above **medical necessity criteria** **MUST** be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### CPT Codes

CPT codes:	Code Description
96900	Actinotherapy (ultraviolet light)
96910	Photochemotherapy; tar and ultraviolet B (Goeckerman treatment) or petrolatum and ultraviolet B

The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT codes above if **medical necessity criteria** are met:

### ICD-10 Diagnosis Codes

ICD-10CM diagnosis codes:	Code Description
C84.00	Mycosis Fungoides, Unspecified Site

C84.01	Mycosis Fungoides, Lymph Nodes of Head, Face, And Neck
C84.02	Mycosis Fungoides, Intrathoracic Lymph Nodes
C84.03	Mycosis Fungoides, Intra-Abdominal Lymph Nodes
C84.04	Mycosis Fungoides, Lymph Nodes of Axilla and Upper Limb
C84.05	Mycosis Fungoides, Lymph Nodes of Inguinal Region and Lower Limb
C84.06	Mycosis Fungoides, Intrapelvic Lymph Nodes
C84.07	Mycosis Fungoides, Spleen
C84.08	Mycosis Fungoides, Lymph Nodes of Multiple Sites
C84.09	Mycosis Fungoides, Extranodal And Solid Organ Sites
C84.A0	Cutaneous T-cell lymphoma, unspecified, unspecified site
H02.731	Vitiligo of right upper eyelid and periocular area
H02.732	Vitiligo of right lower eyelid and periocular area
H02.733	Vitiligo of right eye, unspecified eyelid and periocular area
H02.734	Vitiligo of left upper eyelid and periocular area
H02.735	Vitiligo of left lower eyelid and periocular area
H02.736	Vitiligo of left eye, unspecified eyelid and periocular area
H02.739	Vitiligo of unspecified eye, unspecified eyelid and periocular area
L20.0	Besnier'S Prurigo
L20.81	Atopic Neurodermatitis
L20.82	Flexural Eczema
L20.84	Intrinsic (Allergic) Eczema
L20.89	Other Atopic Dermatitis
L20.9	Atopic dermatitis, unspecified
L25.9	Unspecified Contact Dermatitis, Unspecified Cause
L28.0	Lichen Simplex Chronicus
L28.1	Prurigo Nodularis
L28.2	Other Prurigo
L29.0	Pruritus ani
L29.1	Pruritus scroti
L29.2	Pruritus vulvae
L29.3	Anogenital pruritus, unspecified
L29.8	Other Pruritus
L29.9	Pruritus, Unspecified
L30.0	Nummular dermatitis
L30.1	Dyshidrosis [Pompholyx]
L30.9	Dermatitis, unspecified
L40.0	Psoriasis Vulgaris
L40.1	Generalized Pustular Psoriasis
L40.2	Acrodermatitis Continua
L40.3	Pustulosis Palmaris Et Plantaris
L40.4	Guttate Psoriasis
L40.8	Other Psoriasis
L40.9	Psoriasis, unspecified
L41.0	Pityriasis Lichenoides Et Varioliformis Acuta
L41.1	Pityriasis Lichenoides Chronica
L41.3	Small plaque parapsoriasis
L41.4	Large plaque parapsoriasis
L41.5	Retiform parapsoriasis
L41.8	Other Parapsoriasis
L41.9	Parapsoriasis, unspecified
L43.0	Hypertrophic lichen planus
L43.1	Bullous lichen planus
L43.2	Lichenoid drug reaction



L43.3	Subacute (active) lichen planus
L43.8	Other Lichen Planus
L43.9	Lichen planus, unspecified
L63.0	Alopecia (capitis) totalis
L63.1	Alopecia universalis
L63.2	Ophiasis
L63.8	Other alopecia areata
L63.9	Alopecia areata, unspecified
L66.1	Lichen Planopilaris
L80	Vitiligo
L94.5	Poikiloderma vasculare atrophicans
L98.1	Factitial Dermatitis
Q82.2	Congenital cutaneous mastocytosis

The above **medical necessity criteria** **MUST** be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### CPT Codes

HCPSC code:	Code Description
E0694	Ultraviolet multidirectional light therapy system in 6 ft cabinet, includes bulbs/lamps, timer, and eye protection

The following ICD Diagnosis Codes are considered medically necessary when submitted with the HCPSC code above if **medical necessity criteria** are met:

### ICD-10 Diagnosis Codes

ICD-10CM diagnosis codes:	Code Description
L40.0	Psoriasis Vulgaris
L40.1	Generalized Pustular Psoriasis
L40.2	Acrodermatitis Continua
L40.3	Pustulosis Palmaris Et Plantaris
L40.4	Guttate Psoriasis
L40.8	Other Psoriasis

The above **medical necessity criteria** **MUST** be met for the following code to be covered for targeted phototherapy for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### CPT Codes

HCPSC code:	Code Description
96999	Unlisted special dermatological service or procedure

The above **medical necessity criteria** **MUST** be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### CPT Codes

CPT codes:	Code Description
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96912	Photochemotherapy; psoralens, and ultraviolet A (PUVA)
96920	Laser treatment for inflammatory skin disease (psoriasis); total area less than 250 sq cm
96921	Laser treatment for inflammatory skin disease (psoriasis); 250 sq cm to 500 sq cm
96922	Laser treatment for inflammatory skin disease (psoriasis); over 500 sq cm

The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT codes above if medical necessity criteria are met:

### ICD-10 Diagnosis Codes

ICD-10CM diagnosis codes:	Code Description
L40.0	Psoriasis Vulgaris
L40.1	Generalized Pustular Psoriasis
L40.2	Acrodermatitis Continua
L40.3	Pustulosis Palmaris Et Plantaris
L40.4	Guttate Psoriasis
L40.8	Other Psoriasis
L40.9	Psoriasis, unspecified

The above medical necessity criteria **MUST** be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### CPT Codes

HCPSC code:	Code Description
E0691	Ultraviolet light therapy system, includes bulbs/lamps, timer and eye protection; treatment area 2 sq ft or less

The following ICD Diagnosis Codes are considered medically necessary when submitted with the HCPSC code above if medical necessity criteria are met:

### ICD-10 Diagnosis Codes

ICD-10CM diagnosis codes:	Code Description
L40.0	Psoriasis Vulgaris
L40.2	Acrodermatitis Continua
L40.3	Pustulosis Palmaris Et Plantaris
L40.4	Guttate Psoriasis
L40.8	Other Psoriasis
L40.9	Psoriasis, unspecified

### Description

Light therapy for psoriasis includes both targeted phototherapy and photochemotherapy with psoralen plus ultraviolet A (PUVA). Targeted phototherapy describes the use of ultraviolet light that can be focused on specific body areas or lesions. PUVA uses a psoralen derivative in conjunction with long wavelength ultraviolet A (UVA) light (sunlight or artificial) for photochemotherapy of skin conditions.

### Background

Psoralens with UVA uses a psoralen derivative in conjunction with long wavelength UVA light (sunlight or artificial) for photochemotherapy of skin conditions. Psoralens are tricyclic furocoumarins that occur in

certain plants and can also be synthesized. They are available in oral and topical forms. Oral PUVA is generally given 1.5 hours before exposure to UVA radiation. Topical PUVA therapy refers to directly applying the psoralen to the skin with subsequent exposure to UVA light. Bath PUVA is used in some European countries for generalized psoriasis, but the agent used, trimethylpsoralen, is not approved by the U.S. Food and Drug Administration (FDA). Paint PUVA and soak PUVA are other forms of topical application of psoralen and are often used for psoriasis localized to the palms and soles. In paint PUVA, 8-methoxypsoralen (8-MOP) in an ointment or lotion form is put directly on the lesions. With soak PUVA, the affected areas of the body are placed in a basin of water containing psoralen. With topical PUVA, UVA exposure is generally administered within 30 minutes of psoralen application.

Vitiligo is an idiopathic skin disorder that causes depigmentation of sections of skin, most commonly on the extremities. Depigmentation occurs because melanocytes are no longer able to function properly. The cause of vitiligo is unknown; it is sometimes considered an autoimmune disease. The most common form of the disorder is nonsegmental vitiligo in which depigmentation is generalized, bilateral, symmetrical, and increases in size over time. In contrast, segmental vitiligo, also called asymmetric or focal vitiligo, covers a limited area of skin. The typical natural history of vitiligo involves stepwise progression with long periods in which the disease is static and relatively inactive, and relatively shorter periods in which areas of pigment loss increase.

PUVA has most commonly been used to treat severe psoriasis, for which there is no generally accepted first-line treatment. Each treatment option (eg, systemic therapies such as methotrexate, phototherapy, biologic therapies) has associated benefits and risks. Common minor toxicities associated with PUVA include erythema, pruritus, irregular pigmentation, and gastrointestinal tract symptoms; these generally can be managed by altering the dose of psoralen or UV light. Potential long-term effects include photoaging and skin cancer, particularly squamous cell carcinoma and possibly malignant melanoma. PUVA is generally considered more effective than targeted phototherapy for the treatment of psoriasis. However, the requirement of systemic exposure and the higher risk of adverse reactions (including a higher carcinogenic risk) have generally limited PUVA therapy to patients with more severe cases.

Potential advantages of targeted phototherapy include the ability to use higher treatment doses and to limit exposure to surrounding tissue. Broadband ultraviolet B (BB-UVB) devices, which emit wavelengths from 290 to 320 nm, have been largely replaced by narrowband (NB)-UVB devices. NB-UVB devices eliminate wavelengths below 296 nm, which are considered erythemogenic and carcinogenic but not therapeutic. NB-UVB is more effective than BB-UVB and approaches PUVA in efficacy. Original NB-UVB devices consisted of a Phillips TL-01 fluorescent bulb with a maximum wavelength ( $\lambda_{\text{max}}$ ) at 311 nm. Subsequently, xenon chloride (XeCl) lasers and lamps were developed as targeted NB-UVB treatment devices; they generate monochromatic or very narrow band radiation with a  $\lambda_{\text{max}}$  of 308 nm. Targeted phototherapy devices are directed at specific lesions or affected areas, thus limiting exposure to the surrounding normal tissues. They may therefore allow higher dosages compared with a light box, which could result in fewer treatments to produce clearing.

The original indication of the excimer laser was for patients with mild to moderate psoriasis, defined as involvement of less than 10% of the skin. Typically, these patients have not been considered candidates for light box therapy, because the risks of exposing the entire skin to the carcinogenic effects of UVB light may outweigh the benefits of treating a small number of lesions. Newer XeCl laser devices are faster and more powerful than the original models, which may allow treatment of patients with more extensive skin involvement, 10% to 20% of body surface area. The American Academy of Dermatology does not recommend phototherapy for patients with mild localized psoriasis whose disease can be controlled with topical medications. A variety of topical agents are available including steroids, coal tar, vitamin D analogs (eg, calcipotriol and calcitriol), tazarotene, anthralin).

## Summary

For individuals who have vitiligo who receive targeted phototherapy, the evidence includes systematic reviews of randomized controlled trials (RCTs), 2 individual RCTs, and 2 retrospective studies. Relevant outcomes are a change in disease status, quality of life, and treatment-related morbidity. Individual studies tend to have small sample sizes, and few were designed to isolate the effect of laser therapy. Two

meta-analyses were attempted; however, results from a meta-analysis could not be verified because the selected studies were not available in English, and 1 estimate was imprecise due to the small number of studies and participants. Randomized controlled trials have shown targeted phototherapy to be associated with statistically significant improvements in Vitiligo Area Scoring Index scores and/or repigmentation compared to alternate treatment options. However, 1 of the RCTs only showed marginal differences between groups in these outcomes, limiting clinical significance; the second compared phototherapy to oral vitamin E, which is not an optimal comparator. Overall, there is a lack of clinical trial evidence that compares targeted phototherapy with more conservative treatments or no treatment/placebo. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have vitiligo who have not responded to conservative therapy who receive PUVA (photochemotherapy), the evidence includes systematic reviews and RCTs. There is some evidence from randomized studies, mainly those published before 1985, that PUVA is more effective than a placebo for treating vitiligo. When compared with NB-UVB in meta-analyses, results have shown that patients receiving NB-UVB experienced higher rates of repigmentation than patients receiving PUVA, though the differences were not statistically significant. Based on the available evidence and clinical guidelines, PUVA may be considered in patients with vitiligo who have not responded adequately to conservative therapy.

During psoralen plus ultraviolet A (PUVA) therapy, the patient needs to be assessed on a regular basis to determine the effectiveness of the therapy and the development of side effects. These evaluations are essential to ensure that the exposure dose of radiation is kept to the minimum compatible with adequate control of the disease. Therefore, PUVA is generally not recommended for home therapy.

Targeted phototherapy describes the use of ultraviolet light that can be focused on specific body areas or lesions. The literature supports the use of targeted phototherapy for the treatment of moderate to severe psoriasis comprising less than 20% body area for which narrowband ultraviolet B (NB-UVB) or photochemotherapy with psoralen plus ultraviolet A (PUVA) are indicated, and for the treatment of mild to moderate localized psoriasis that is unresponsive to conservative treatment. Based on this review, evidence is lacking for the use of targeted phototherapy for the first-line treatment of mild psoriasis or for the treatment of generalized psoriasis or psoriatic arthritis.

Evidence from randomized controlled trials suggests that PUVA is at least as effective as NB-UVB for patients with moderate to severe psoriasis. In addition, PUVA for severe treatment-resistant psoriasis is well-accepted and is recommended by the American Academy of Dermatology. There is a lack of evidence that home-based PUVA for treating psoriasis is as safe or effective as office-based treatment.

#### **Home Narrow Band UV-B phototherapy system (handheld units)**

In a randomized controlled trial, Koek (2009) reported on a multicenter single blind randomized clinical trial of 196 patients from 14 medical centers. The main outcome measure is effectiveness. PASI 50 and SAPASI 50: a 50% or more improvement of the baseline PASI or SAPASI considered relevant treatment effect; PASI 75 and SAPASI 75: a 75% improvement of the PASI and SAPASI considered successful treatment effect; PASI 90 and SAPASI 90: a 90% of the PASI and SAPASI (almost complete clearance) and a patient assessed visual severity assessment scale ranging from 0 (no psoriasis) to 100 (most severe psoriasis imaginable) were measured.

Of the 94 patients who did home therapy, 81.9% of them judged their psoriasis to have improved 50% or more; 69.1% of them judged their psoriasis to have improved 75% or more; 43.6% of them judged their psoriasis to have improved 90% or more. The study concluded that based on the outcome measures, both home phototherapy and standard office-based phototherapy are equally effective, and patients express a preference for home treatment. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

*PASI: Psoriasis area severity index; SAPASI: self-administered psoriasis area severity index*

## Policy History

Date	Action
1/2024	Annual review. References updated. Policy statements unchanged.
8/2023	Clarifications made to description and summary section. Policy statements unchanged.
2/2023	Annual review. References added. Policy statements unchanged.
2/2022	References added. Policy statements unchanged.
1/2021	Medicare information removed. See MP #132 Medicare Advantage Management for local coverage determination and national coverage determination reference.
6/2020	Medically necessary and investigational indications described for home narrow band UV-B phototherapy system (handheld units) for moderate-to-severe localized psoriasis. The policy is also clarified stating coverage for either the home UV-B booth or the home narrow band UV-B handheld unit. We will not cover both devices simultaneously. Clarified coding information. Effective 6/1/2020.
2/2019	Targeted Phototherapy for psoriasis transferred from medical policy #698 Light Therapy for Psoriasis. Coverage unchanged.
1/2018	Medically necessary statement on targeted phototherapy clarified. Clarified coding information. 1/1/2018.
10/2017	Clarified coding information. Added information regarding treatment of vitiligo from policy #911 Light Therapy for Vitiligo. Policy #911 retired. Effective 10/1/2017.
4/2017	Clarified coding information.
4/2016	Policy clarified to indicate coverage for UV-B phototherapy for mycosis fungoides. Clarified coding information. 4/1/2016
4/2016	Phototherapy statements transferred from medical policy #698, Light Therapy for Psoriasis. 4/2016. Clarified coding information.
3/2015	Annual review. New references added.
3/2015	UV-B phototherapy indications clarified.
10/2014	Language on Light Therapy for Psoriasis transferred from medical policy #059, Phototherapy to medical policy #698. Clarified: <ul style="list-style-type: none"> <li>o Treatment of vitiligo on the face, neck and hands transferred to medical policy #911, Light Therapy for Vitiligo.</li> <li>o Home phototherapy for neonatal jaundice language removed, treatment is medically necessary.</li> <li>o PUVA for graft versus host disease language for Medicare Advantage members removed. There is no Medicare Local Coverage Determination or National Coverage Determination.</li> </ul>
5/3/2012	Annual review. New references added.
11/2011	Reviewed - Medical Policy Group - Plastic Surgery and Dermatology, no changes in coverage.
5/2011	Reviewed - Medical Policy Group - Pediatrics, no changes in coverage.
12/2010	Reviewed - Medical Policy Group - Plastic Surgery and Dermatology, no changes in coverage.
5/2010	Reviewed - Medical Policy Group - Pediatrics, no changes in coverage.
4//2010	Clarified UV-B language and covered indications. Effective 4/24/2010.
4/2010	Annual review. New references added.
12/2009	Reviewed - Medical Policy Group - Plastic Surgery and Dermatology, no changes in coverage.
6/2009	Clarified coverage for pityriasis lichenoides chronica.
5/2009	Reviewed - Medical Policy Group - Pediatrics, no changes in coverage.
12/2008	Reviewed - Medical Policy Group - Plastic Surgery and Dermatology, no changes in coverage.
11/2008	Added coverage for PUVA for dyshidrosis diagnosis.
5/2008	Reviewed - Medical Policy Group - Pediatrics, no changes in coverage.
4/2008	Added coverage for mild to moderate psoriasis that is unresponsive to conservative therapy and moderate to severe localized psoriasis, comprising less than 20% body areas.

12/2007	Reviewed - Medical Policy Group - Plastic Surgery and Dermatology, no changes in coverage.
5/2007	Reviewed - Medical Policy Group - Pediatrics - Added statement regarding a rapid worsening of neonatal jaundice.
12/2006	Reviewed - Medical Policy Group - Plastic Surgery and Dermatology, no changes in coverage.
12/2006	Coverage indications for UVB were clarified. Clarified coverage exclusion of xenon chloride excimer laser for phototherapeutic treatment of psoriasis.
5/2006	Reviewed - Medical Policy Group - Pediatrics, no changes in coverage.
12/2005	Reviewed - Medical Policy Group - Plastic Surgery and Dermatology, no changes in coverage.
5/2005	Reviewed - Medical Policy Group - Pediatrics, no changes in coverage.
1/2005	Clarified coverage statement for PUVA treatment for graft-versus-host disease for Medicare HMO Blue members.
5/2004	Reviewed - Medical Policy Group - Pediatrics, no changes in coverage.
12/2003	Reviewed - Medical Policy Group - Plastic Surgery and Dermatology, no changes in coverage.
11/2003	Reviewed - Medical Policy Group - Pediatrics, no changes in coverage.
2/1999	Added coverage for home UV-B booth for patients with severe psoriasis who require frequent ultraviolet light treatments but are unable to travel. Effective 3/1/1999.
8/1998	Clarified billing information for the following forms of phototherapy: lamp, light panel, or special blanket.
2/1998	Remove criteria for home phototherapy for neonatal jaundice.
8/1997	Added coverage for PUVA treatment for graft-versus-host disease for Medicare HMO Blue members.
10/1995	Medical Policy issued.

## Information Pertaining to All Blue Cross Blue Shield Medical Policies

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[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

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## Endnotes

<sup>1</sup> PUVA policy issued 12/95 based in part on the American Academy of Dermatology Guidelines of Care for Phototherapy and Photochemotherapy (Journal of American Academy of Dermatology 1994; 31:643-8). Also see the clinical review Photochemotherapy beyond psoriasis (Honig et al., Journal of American Academy of Dermatology 1994; 31:775-90) for additional information.

<sup>2</sup> FDA-approved devices. Note: this is not an all-inclusive list. In 2001, a XeCl excimer laser (XTRAC™ by PhotoMedex) received 510(k) clearance from FDA for the treatment of mild to moderate psoriasis. The 510(k) clearance has subsequently been obtained for a number of targeted UVB lamps and lasers, including newer versions of the XTRAC system including the XTRAC Ultra™, the VTRAC™ lamp (PhotoMedex), the BCclear™ lamp (Lumenis), and the European manufactured Excilite™ and Excilite μ™ XeCl lamps. The oral psoralen products Oxsoralen-Ultra (methoxsalen soft gelatin capsules) and 8-MOP (methoxsalen hard gelatin capsules) have been approved by FDA; both are made by Valeant Pharmaceuticals. Topical psoralen products have also received FDA approval eg, Oxsoralen (Valeant Pharmaceuticals).

<sup>3</sup> Based on expert opinion

<sup>4</sup> Blue Cross Blue Shield Association MPRM #2.01.47

<sup>5</sup> Blue Cross Blue Shield Association MPRM #2.01.86

# Vitiligo

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## Policy

### Scope of Policy

This Clinical Policy Bulletin addresses vitiligo.

#### I. Medical Necessity

Aetna considers the following established methods medically necessary for the treatment of vitiligo:

- Excimer laser (e.g., XTRAC, PhotoMedex, Radnor, PA; EX-308, Ra Medical Systems, Inc., Carlsbad, CA)
- Narrow-band ultraviolet B (NB-UVB)
- Topical and oral psoralen photochemotherapy (PUVA)
- Topical tacrolimus
- Topical and systemic corticosteroids.

Aetna considers continued PUVA or narrow-band UVB therapy not medically necessary unless there is significant follicular pigmentation after 6 months of therapy (8 to 10 treatments per month).

#### II. Experimental and Investigational

Aetna considers the following procedures experimental and investigational because the effectiveness of these approaches has not been established:

- A. ApaI, BsmI, catalase (389C>T), cystathionine B synthase (CBS), cytotoxic T-lymphocyte antigen (CTLA)-4+49A/G, human leukocyte antigen-A, NLRP1, methylenetetrahydrofolate reductase



- (MTHFR), protein tyrosine phosphatase, non-receptor type 22 +1858C→T, and TNF-alpha-308G/A gene polymorphisms testing for early detection of vitiligo
- B. Measurement of interleukin-17 (IL-17) levels for the management of vitiligo
- C. Use of digital and analog image analysis systems (e.g., 2D digital imaging analysis and 3D photography) for surface calculation of vitiligo lesions
- D. The following interventions for the treatment of vitiligo (not an all-inclusive list):

- Apremilast (alone or combined with NB-UVB)
- Autologous mini-punching grafting
- Blister roof grafting (suction epidermal blister grafting) (e.g., CelluTome Epidermal Harvesting System)
- Capecitabine
- Carbon dioxide fractional laser
- Chimeric monoclonal antibody to CD20 (e.g., rituximab)
- Fire needle therapy
- Glutathione
- Home phototherapy
- Interleukins
- Intradermal mesotherapy (injections of bio-revitalizant NCTF135)
- Melagenine
- $\alpha$ -melanocyte stimulating hormone (e.g., afamelanotide)
- Melanocyte transplantation/cultured and non-cultured cellular melanocyte keratinocyte transfer
- Neovir (an intramuscular immunomodulatory agent, composed of sodium oxodihydroacridinylacetate)
- Prostaglandins (e.g., bimatoprost, latanoprost, and prostaglandin E2)
- Split thickness skin grafting
- Tars
- Topical minoxidil
- Topical phenytoin gel
- Topical pseudocatalase
- Tumor necrosis factor-alpha agents (e.g., adalimumab, etanercept, and infliximab)
- Vitamin D analogs (e.g., calcitriol and paricalcitol).

### III. Cosmetic

Aetna considers treatments for vitiligo cosmetic if they do not affect the underlying condition and do not result in improved protection against skin cancer; specifically micropigmentation (tattooing) and depigmentation (with monobenzyloether of hydroquinone/monobenzone) are considered cosmetic.


### IV. Related Policies

For janus kinase inhibitors (e.g., ruxolitinib [Opzelura]), see pharmacy benefit plans.

Table:

## CPT Codes / HCPCS Codes / ICD-10 Codes

**CPT codes covered if selection criteria are met:**

 Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	Code Description
96900	Actinotherapy (ultraviolet light) F [Narrow-hyphenhyphenonly">hyphenband ultraviolet B (NB-hyphenhyphenonly">hyphenUVB)]
96912	Photochemotherapy; psoralens and ultraviolet A (PUVA)
96913	Photochemotherapy (Goeckerman and/or PUVA) for severe photoresponsive dermatoses requiring at least four to eight hours of care under direct supervision of the physician (includes application of medication and dressings)
96999	Unlisted special dermatological service or procedure [excimer laser]

### CPT codes not covered for indications listed in the CPB:

***Cytotoxic T-hyphenhyphenlymphocyte antigen (CTLA)-hyphenhyphen4+49A/G and TNF-hyphenhyphenalpha 308G/A polymorphism testing, cystathionine B synthase (CBS) gene polymorphism, measurement of Interleukin-hyphenhyphen17 levels - hyphenhyphenonly">hyphen no specific code:***

11920 - hyphenhyphenonly">hyphen 11922	Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation
15100	Split-hyphenhyphenonly">hyphenthickness autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children (except 15050)
15101	each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
76376	3D rendering with interpretation and reporting of computed tomography, magnetic resonance imaging, ultrasound, or other tomographic modality with image postprocessing under concurrent supervision; not requiring image postprocessing on an independent workstation
76377	requiring image postprocessing on an independent workstation
81291	MTHFR (5,10-hyphenhyphenonly">hyphenmethylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
97810	Acupuncture, 1 or more needles; without electrical stimulation, initial 15 minutes of personal one-hyphenhyphenonly">hyphenhyphenon-hyphenhyphenonly">hyphenhyphenone contact with patient [fire needle therapy]
97811	without electrical stimulation, each additional 15 minutes of personal one-hyphenhyphenonly">hyphenhyphenon-hyphenhyphenonly">hyphenhyphenone contact with the patient, with re-hyphenhyphenonly">hyphenhypheninsertion of needle(s) (List separately in addition to code for primary procedure) [fire needle therapy]

**Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":**

Code	Code Description
<b>HCPCS codes covered if selection criteria are met:</b>	
J0702	Injection, betamethasone acetate 3mg and betamethasone sodium phosphate, 3 mg
J1020	Injection, methylprednisolone acetate, 20 mg
J1030	Injection, methylprednisolone acetate, 40 mg
J1040	Injection, methylprednisolone acetate, 80 mg
J1094	Injection, dexamethasone acetate, 1 mg
J1100	Injection, dexamethasone sodium phosphate, 1mg
J1700	Injection, hydrocortisone acetate, up to 25 mg (i. e., Hydrocortone acetate)
J1710	Injection, hydrocortisone sodium phosphate, up to 50 mg (i.e., Hydrocortone phosphate)
J1720	Injection, hydrocortisone sodium succinate, up to 100 mg (i.e., Solu-hyphenhyphenonly">hyphenCortef)
J2650	Injection, prednisolone acetate, up to 1 ml (i.e., Key-hyphenhyphenonly">hyphenPred 25, Key-hyphenhyphenonly">hyphenPred 50, Predcor-hyphenhyphenonly">hyphen25, Predcor-hyphenhyphenonly">hyphen50, Predoject 50, Predalone-hyphenhyphenonly">hyphen50, Predicort-hyphenhyphenonly">hyphen50)
J2920	Injection, methylprednisolone sodium succinate, up to 40 mg (i.e., Solu-hyphenhyphenonly">hyphenMedrol)
J2930	Injection, methylprednisolone sodium succinate, up to 125 mg (i.e., Solu-hyphenhyphenonly">hyphenMedrol)
J3301	Injection, triamcinolone acetonide, per 10 mg (i.e., Kenalog)
J3302	Injection, triamcinolone diacetate, per 5 mg (i.e., Aristocort)
J3303	Injection, triamcinolone hexacetonide, per 5 mg (i.e., Aristospan)
J7509	Methylprednisolone, oral, per 4 mg
J7510	Prednisolone, oral, per 5 mg
J7512	Prednisone, immediate release or delayed release, oral, 1 mg
J8540	Dexamethasone, oral, 0.25 mg

**HCPCS codes not covered for indications listed in the CPB:**

***Apremilast, Intradermal mesotherapy (injections of bio-hyphenhyphenonly">hyphenrevitalizant NCTF135)-hyphenhyphenonly">hyphen no specific code***

A4633	Replacement bulb/lamp for ultraviolet light therapy system, each
E0691	Ultraviolet light therapy system panel, includes bulbs/lamps, timer, and eye protection; treatment area two square feet or less
E0692	Ultraviolet light therapy system panel, includes bulbs/lamps, timer, and eye protection, four foot panel
E0693	Ultraviolet light therapy system panel, includes bulbs/lamps, timer, and eye protection, six foot panel

**Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":**

<b>Code</b>	<b>Code Description</b>
E0694	Ultraviolet multidirectional light therapy system in 6 foot cabinet, includes bulbs/lamps, timer, and eye protection
J0135	Injection, adalimumab, 20 mg
J0636	Injection, calcitriol, 0.1 mcg
J1438	Injection, etanercept, 25 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-hyphenhyphenonly">hyphenadministered)
J1745	Injection, infliximab, 10 mg
J2501	Injection, paricalcitol, 1 mcg
J9312	Injection, rituximab, 10 mg
Q5103	Injection, infliximab-hyphenhyphenonly">hyphendyyb, biosimilar, (Inflectra), 10 mg
Q5104	Injection, infliximab-hyphenhyphenonly">hyphenabda, biosimilar, (Renflexis), 10 mg
Q5109	Injection, infliximab-hyphenhyphenonly">hyphenqbtx, biosimilar, (Ixifi), 10 mg
Q5131	Injection, adalimumab-hyphenhyphenonly">hyphenaacf (idacio), biosimilar, 20 mg
S0161	Calcitriol, 0.25 mcg

**ICD-hyphenhyphenonly">hyphen10 codes covered if selection criteria are met:**

L80	Vitiligo
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**Human leukocyte antigen-hyphenhyphenonly">hyphenA polymorphism testing - hyphenhyphenonly">hyphen no specific code:**

**ICD-hyphenhyphenonly">hyphen10 codes not covered for indications listed in the CPB (not all-hyphenhyphenonly">hypheninclusive):**

L80	Vitiligo
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**Protein tyrosine phosphatase:**

**CPT codes not covered for indications listed in the CPB:**

86341	Islet cell antibody
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**Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":**

**Code**

**Code Description**

**ICD-hyphenhyphenonly">hyphen10 codes not covered for indications listed in the CPB (not all-hyphenhyphenonly">hypheninclusive):**

L80 Vitiligo

**NLPR1 gene polymorphisms testing -hyphenhyphenonly">hyphen no specific code:**

**ICD-hyphenhyphenonly">hyphen10 codes not covered for indications listed in the CPB (not all-hyphenhyphenonly">hypheninclusive):**

L80 Vitiligo  
M30.0 -  
hyphenhyphenonly">hyphen Polyarteritis nodosa and related conditions  
M35.9

**CelluTome Epidermal Harvesting System:**

**CPT codes not covered for indications listed in the CPB:**

15110	Epidermal autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children
15111	Epidermal autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15115	Epidermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children
15116	Epidermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

**ICD-hyphenhyphenonly">hyphen10 codes not covered for indications listed in the CPB (not all-hyphenhyphenonly">hypheninclusive):**

L80 Vitiligo

**Prostaglandins and prostaglandin E2:**



*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

Code	Code Description
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**CPT codes not covered for indications listed in the CPB:**

84150	Prostaglandin, each
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**ICD-hyphenhyphenonly">hyphen10 codes not covered for indications listed in the CPB (not all-hyphenhyphenonly">hypheninclusive):**

L80	Vitiligo
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*Aprimalist, Topical phenytoin gel, Glutathion, Melagenin, Topical minoxidil, Topical pseudocatalase, Nevoir, Carbon dioxide fractional laser -hyphenhyphenonly">hyphen no specific code:*

**ICD-hyphenhyphenonly">hyphen10 codes not covered for indications listed in the CPB (not all-hyphenhyphenonly">hypheninclusive):**

L80	Vitiligo
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***Capecitabine:***

**HCPCS codes not covered for indications listed in the CPB:**


J2355	Injection, oprelvekin, 5 mg
J8520	Capecitabine, oral, 150 mg
J8521	Capecitabine, oral, 500 mg
J9015	Injection, aldesleukin, per single use vial

**ICD-hyphenhyphenonly">hyphen10 codes not covered for indications listed in the CPB (not all-hyphenhyphenonly">hypheninclusive):**

L80	Vitiligo
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## Background



 Vitiligo is an acquired pigmentary disorder of skin and mucous membranes, manifesting itself by expanding depigmented lesions. While the cause is not well understood, the observed variation in clinical manifestations of the condition has suggested several possible etiologies, including association with other medical conditions. The 3 prevailing theories of the pathogenesis of vitiligo include an immune hypothesis, a neural-mediated hypothesis, and a “self-destruct” hypothesis. These 3, plus newer hypotheses suggesting that vitiligo may be due to a melanocyte growth factor deficiency or to an abnormal melatonin receptor on melanocytes, have not been definitively proven, and it is likely that the loss of epidermal and follicular melanocytes in vitiligo may be the result of several different pathogenic mechanisms.

Psoralen photochemotherapy (psoralen and ultraviolet light A or PUVA) is appropriate for properly selected patients with vitiligo. The treatment involves taking oral psoralen or applying it topically followed by carefully timed exposure to UVA. Repigmentation may begin after 15 to 25 treatments. Approximately 50 % of patients will develop repigmentation after 150 to 200 PUVA treatments over 12 to 24 months. The response is slow and repigmentation may not be complete. Response to PUVA is unlikely to occur if follicular pigmentation has not appeared after 3 months of PUVA therapy. Dark-skinned patients respond better than fair skin patients do; the latter are unlikely to benefit from PUVA unless there is marked disfigurement. Most patients who respond do not develop new areas of pigment loss; furthermore, maintenance with PUVA therapy is not necessary.


Children under age 10 are generally not treated with oral phototherapy; instead, a mild topical corticosteroid cream is often prescribed. A stronger topical corticosteroid cream can be prescribed for adults. Patients must apply the cream (e.g., triamcinolone 0.1 %, desonide 0.05 %) once-daily to the white patches on their skin for at least 3 to 4 months before seeing any results. Systemic corticosteroids can stop the progression of vitiligo for some patients, but may also produce unacceptable side effects. Oral mini-pulse therapy with 5 mg betamethasone/dexamethasone may stop the progression and induce spontaneous repigmentation in some vitiligo patients.

A number of recently published studies have demonstrated that narrow-band UVB is an effective treatment for vitiligo, and compares favorably to UVA and psoralens (e.g., Westerhof, 1997; Njoo et al, 2000; Scherschun et al, 2001). Unlike PUVA, narrow-band UVB does not involve the use of sensitizing agents. Narrow-band UVB is typically administered 2 to 3 times per week for several months. However, there is a lack of evidence regarding the safety and effectiveness of home narrow-band UVB phototherapy for the treatment of vitiligo.

In a randomized controlled study, Ada et al (2005) concluded that narrow-band UVB phototherapy is effective in treating vitiligo, and the addition of topical calcipotriol does not improve treatment outcome.

In a double-blind randomized study, Yones et al (2007) compared the effectiveness of oral PUVA with that of narrowband-UVB (NB-UVB) phototherapy in patients with non-segmental vitiligo. A total of 56 patients received twice-weekly therapy with PUVA or NB-UVB. The change in body surface area affected by vitiligo and the color match of repigmented skin compared with unaffected skin were assessed after 48 sessions of therapy, at the end of the therapy course, and 12 months after the end of therapy. The results in the 25 patients each in the PUVA and NB-UVB groups who began therapy were analyzed. The median number of treatments was 47 in the PUVA-treated group and 97 in the NB-UVB-treated group ( $p = 0.03$ ); this difference was probably due to differences in effectiveness and adverse effects between the 2 modalities, such that patients in the NB-UVB group wanted a longer course of treatment. At the end of therapy, 16 (64 %) of 25 patients in the NB-UVB group showed greater than 50 % improvement in body surface area affected compared with 9 (36 %) of 25 patients in the PUVA group. The color match of the repigmented skin was excellent in all patients in the NB-UVB group but in only 11 (44 %) of those in the PUVA group ( $p < 0.001$ ). In patients who completed 48 sessions, the improvement in body surface area affected by vitiligo was greater with NB-UVB therapy than with PUVA therapy ( $p = 0.007$ ). Twelve months after the cessation of therapy, the superiority of NB-UVB tended to be maintained. The authors concluded that in the treatment of non-segmental vitiligo, NB-UVB therapy is superior to oral PUVA therapy.

In a randomized, investigator-blinded and half-side comparison study, Casacci and colleagues (2007) compared the effectiveness of NB-UVB phototherapy and 308-nm monochromatic excimer light (MEL) in patients with vitiligo. A total of 21 subjects with symmetrical vitiligo lesions were enrolled in this study. Vitiligo lesions on

 side were treated twice-weekly for 6 months with 308-nm MEL, while NB-UVB phototherapy was used to treat lesions on the opposite side. At the end of the study, 6 lesions (37.5 %) treated with 308-nm MEL and only 1 lesion (6 %) treated with NB-UVB achieved an excellent repigmentation (score 4) while 4 lesions (25 %) treated with 308-nm MEL and 5 lesions (31 %) treated with NB-UVB showed a good repigmentation (score 3). The authors concluded that it appears that 308-nm MEL is more effective than NB-UVB in treating vitiligo lesions and it induces repigmentation more rapidly.


Several clinical studies have demonstrated that the Xenon-Chloride excimer laser is effective in repigmentation of vitiligo patches (Hadi et al, 2004; Choi et al, 2004; Esposito et al, 2004; Kawalek et al, 2004; Taneja et al, 2003; Spencer et al, 2002). The excimer laser may be especially useful in treatment of localized vitiligo that is refractory to topical corticosteroids. Treatments are typically administered twice weekly and up to 60 treatments may generally be medically necessary. Recent studies have also suggested that combination treatment with excimer laser and topical methoxypsoralen resulted in better repigmentation than excimer laser alone. However, due to the small sample sizes in these studies, their findings need to be validated by additional studies (Grimes, 2005).

Transplantation of autologous pigment cells is considered experimental and investigational for the treatment of vitiligo because of a lack of adequate clinical evidence of effectiveness from randomized controlled clinical trials.

van Geel and colleagues (2006) investigated the effectiveness of non-cultured epidermal cell transplantation in treating stabilized vitiligo using objective and subjective evaluation methods. Non-cultured autologous melanocytes and keratinocytes were grafted in a hyaluronic-acid-enriched suspension on superficially laser-abraded vitiligo lesions in 40 patients with refractory stable vitiligo (30 with generalized and 10 with localized vitiligo). The repigmentation was evaluated 3 to 12 months after grafting using a digital image analysis system. Furthermore, the treatment was evaluated from patients' point of view with the DLQI (Dermatology Life Quality Index) and a global assessment. The mean percentage of repigmentation, evaluated at the last follow-up visit, was 72 % (median of 84 %), and a repigmentation of greater than or equal to 70 % was observed in 62 % of patients. The best results were achieved in the neck and the pre-sternal region. A subjective evaluation was performed in 50 % of the subjects. The mean DLQI score at inclusion (6.95, SD = 6.68, n = 20) was significantly lowered after treatment ( $p = 0.013$ , mean 3.85, SD = 4.13, n = 20). The patients were satisfied with the achieved result, and they found it worthwhile to undergo the treatment and would choose it again. The authors concluded that according to both subjective and objective evaluation methods, non-cultured epidermal cell transplantation is promising in patients with stable vitiligo.

In a randomized, double-blind clinical trial, Rodríguez-Martín and colleagues (2009) assessed the safety and effectiveness of tacalcitol (a vitamin D analog) ointment plus sunlight exposure in the treatment of non-segmental vitiligo. A total of 80 patients participated in this study. Effectiveness was assessed by quantification of the lesional re-pigmentation area at the end of the study compared with the baseline. Tacalcitol (n = 40) or matching placebo ointment (n = 40) was applied once-daily at night. Daily exposure to sunlight for 30 mins was performed. Treatment was continued for 4 months. The response of the lesions was clinically verified every 2 weeks by a "blinded" medical investigator. All adverse effects were recorded. Over 16 weeks, 64 patients completed the study requirements. There was no significant difference in the re-pigmentation response at the 16-week time point between the vehicle plus sunlight exposure and the tacalcitol plus sunlight exposure groups. No reduction in the size of the lesions greater than 25 % was observed in the tacalcitol-treated patients. No serious adverse effects were observed. The authors concluded that the combination of tacalcitol with heliotherapy has no additional advantages compared with heliotherapy alone.

In a Cochrane review on interventions for vitiligo, Whitton et al (2010) stated that new interventions include MEL, polypodium leucotomos, melanocyte transplantation, oral anti-oxidants, Chinese zengse pill, and pimecrolimus. These investigators analyzed the data from 28 studies that met their outcome criteria of improvement in quality of life and greater than 75 % repigmentation. A total of 15 analyses from studies comparing various interventions showed a statistically significant difference between the proportions of participants achieving more than 75 % repigmentation. The majority of analyses showing statistically significant differences were from studies that assessed combination interventions that generally included some form of light


 **Attention.** Topical preparations, in particular corticosteroids, reported most adverse effects. However, in the combination studies it was difficult to ascertain which treatment caused these effects. None of the studies was able to demonstrate long-term benefits. Very few studies were conducted on children or included segmental vitiligo. These researchers found 1 study of psychological interventions and none evaluating micropigmentation, depigmentation, or cosmetic camouflage. The authors concluded that this review has found some evidence from individual studies to support existing therapies for vitiligo, but the usefulness of the findings is limited by the different designs and outcome measurements and lack of quality of life measures. There is a need for follow-up studies to assess permanence of repigmentation as well as high quality randomized trials using standardized measures and which also address quality of life.

Alghamdi and colleagues (2012) stated that although the exact pathogenesis of vitiligo is not fully understood, it appears to be an autoimmune disease. It is hypothesized that tumor necrosis factor-alpha (TNF-alpha) plays an important role in vitiligo. Tumor necrosis factor-alpha can destroy melanocytes through the induction of various apoptotic pathways. In addition, TNF-alpha can inhibit melanocyte stem cell differentiation. These researchers evaluated the safety and effectiveness of treating vitiligo patients with anti-TNF-alpha agents. A total of 6 patients were recruited. All patients had widespread non-segmental vitiligo. Biologics, including infliximab, etanercept, and adalimumab, were given according to treatment regimens used for psoriasis. Photographs were taken at the initial visit, every 2 months during the therapy and then 6 months after therapy completion. All patients completed the treatment; 2 patients were treated with infliximab, 2 with etanercept, and 2 with adalimumab. All of the biologics were well-tolerated throughout the treatment period, and none of the patients reported any significant adverse events. Digital images were compared before, during and after treatment. Repigmentation of the vitiliginous areas was not observed in any of the patients. Vitiligo worsened in 1 patient who was treated with infliximab and developed a psoriasiform rash. However, the remaining patients did not develop any new depigmented patches during treatment or at the 6-month follow-up; vitiligo was considered stable in these 5 patients. The authors concluded that although the anti-TNF-alpha agents were well-tolerated in all 6 vitiligo patients, efficacy was not observed. They stated that further evaluation with larger studies may be required.

In a pilot study, Dayel et al (2013) evaluated the safety and effectiveness of alefacept in the treatment of vitiligo. After providing informed written consent, 4 adult patients with widespread vitiligo (covering a body surface area greater than or equal to 5 %) were treated with weekly intra-muscular injections of 15 mg alefacept for 12 weeks. All patients were monitored clinically, by laboratory investigation, and by digital image analysis. All patients were followed-up with for 24 weeks. All patients tolerated alefacept well, without any adverse events. None of the patients showed any re-pigmentation. However, 1 patient developed new de-pigmented patches during treatment with alefacept. The authors concluded that alefacept as a monotherapy for vitiligo treatment did not result in any patient improvement, and further evaluation in larger studies may be required.

Wong and Lin (2013) stated that topical calcineurin inhibitors (e.g., pimecrolimus and tacrolimus) are indicated for the treatment of atopic dermatitis, but they have been studied in many off-label uses. These investigators reviewed the English language literature to define their roles in treatment of vitiligo. Double-blind studies showed that tacrolimus 0.1 % ointment combined with excimer laser is superior to placebo, especially for UV-resistant areas, such as bony prominences of the extremities. When used alone, tacrolimus 0.1 % ointment is almost as effective as clobetasol propionate 0.05 % ointment. Other studies suggested it can also be effective for facial lesions. Double-blind studies showed that pimecrolimus 1 % cream combined with narrow band UVB is superior to placebo, especially for facial lesions. Moreover, the authors concluded that additional studies would further clarify the role of topical calcineurin inhibitors in vitiligo.

An UpToDate review on "Vitiligo" (Goldstein and Goldstein, 2013) states that "Topical calcineurin inhibitors (e.g., tacrolimus, pimecrolimus) may be an effective therapy for vitiligo; however, most of the evidence of their use comes from small case series and uncontrolled trials .... In 2005, the United States Food and Drug Administration (FDA) issued an alert about a possible link between topical tacrolimus and pimecrolimus and cases of lymphoma and skin cancer in children and adults, and in 2006 placed a "black box" warning on the prescribing information for these medications. No definite causal relationship has been established; however, the FDA recommended that these agents only be used as second-line agents for atopic dermatitis. If these agents

 for the treatment of vitiligo, it would be reasonable to follow the additional safety recommendations made by the FDA for their use in atopic dermatitis”.

Grimes et al (2013) noted that many recent studies have demonstrated defects in the melanocortin system in patients with vitiligo, including decreased circulating and lesional skin levels of  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH). Afamelanotide is a potent and longer-lasting synthetic analog of naturally occurring  $\alpha$ -MSH. These investigators described the preliminary results of 4 patients with generalized vitiligo who developed re-pigmentation using afamelanotide in combination with narrowband UV-B (NB-UV-B) phototherapy. Patients were treated 3 times weekly with NB-UV-B and starting in the 2nd month received a series of 4 monthly implants containing 16 mg of afamelanotide. Afamelanotide induced faster and deeper re-pigmentation in each case. All patients experienced follicular and confluent areas of re-pigmentation within 2 days to 4 weeks after the initial implant, which progressed significantly throughout treatment. All patients experienced diffuse hyper-pigmentation. The authors proposed that afamelanotide represents a novel and potentially effective treatment for vitiligo. The combined therapy of NB-UV-B and afamelanotide appears to promote melanoblast differentiation, proliferation, and eumelanogenesis. They stated that further studies are necessary to confirm these observations.

Mulekar and Isedeh (2013) evaluated the evidence for the safety, effectiveness and applicability of the various surgical methods in the treatment of vitiligo. For this systematic review of vitiligo surgical therapies, the searches included: PubMed, MEDLINE and Cochrane databases. These investigators reviewed studies reporting on autologous mini-punching grafting, blister roof grafting (suction epidermal blister grafting), cultured and non-cultured cellular melanocyte keratinocyte transfer, split thickness skin grafting (STSG). While all methods vary in their re-pigmentation outcomes, STSG is found to have the highest re-pigmentation success rate. Overall, post-operative complications included milia, scarring, cobblestone appearance or hyper-pigmentation of treated areas. The authors concluded that this review highlighted the need for more randomized controlled trials in this field, under-pinned by a more standardized objective approach to the assessment of re-pigmentation following surgical interventions.

Al Jasser (2013) reported the benefit of autologous non-cultured melanocyte-keratinocyte transplantation (MKT) in patients with vitiligo-associated leukotrichia. All 4 patients showed significant re-pigmentation in vitiligo-associated leukotrichia after MKT. The authors concluded that melanocyte-keratinocyte transplantation may represent a good therapeutic option for the re-pigmentation of vitiligo-associated leukotrichia. Moreover, they stated that larger prospective studies are needed to determine the true response rate and mechanism of re-pigmentation.

In a pilot study, Ruiz-Arguelles et al (2013) reported the findings of treatment of vitiligo with a chimeric monoclonal antibody to CD20. Five patients with active disseminated vitiligo were given 1 g of a chimeric (murine/human) monoclonal antibody to CD20 in a single intravenous infusion and followed-up for 6 months. Three of the patients showed an overt clinical and histological improvement of the disease, 1 presented slight improvement and the remaining patient showed no changes. Improvement was neither associated with changes in laboratory parameters nor to a specific human leucocyte antigen D-related (HLA-DR) phenotype. The authors concluded that these preliminary results were encouraging, and further clinical trials should be undertaken.

Furthermore, an UpToDate review on “Vitiligo” (Goldstein and Goldstein, 2014) does not mention the use of chimeric monoclonal antibody to CD20/rituximab as a therapeutic option.

The British Association of Dermatologists’ guideline on “The diagnosis and management of vitiligo” (Gawkrodger et al, 2008), which have been cited by the American Academy of Dermatology, stated that topical pimecrolimus or tacrolimus should be considered as alternatives to the use of a highly potent topical steroid in view of their better short-term safety profile. Furthermore, the European Dermatology Forum guideline on “Vitiligo” also recommended the use of calcineurin inhibitors as first-line therapy for segmental vitiligo or limited non-segmental Vitiligo (less than 2 to 3 % of body surface).





## **Combination of Topical Calcineurin Inhibitors and Phototherapy for the Treatment of Vitiligo**

In a meta-analysis, Dang et al (2016) examined the effect of topical calcineurin inhibitors as monotherapy or combined with phototherapy for vitiligo treatment. These investigators searched the MEDLINE, Embase, and Cochrane central register of controlled trials databases for articles published prior to September 2014. A total of 13 studies were included in the meta-analysis. After pooling the trials, these researchers concluded that calcineurin inhibitors showed a better therapeutic effect on vitiligo than placebo, according to lesion report (risk ratio [RR] = 2.62, 95 % confidence interval [CI]: 1.39 to 4.93,  $p = 0.003$ ) and patient report (RR = 1.42, 95 % CI: 0.87 to 2.31,  $p = 0.157$ ). Subgroup analysis was performed to examine if the combination with phototherapy was a source of heterogeneity. The trial sequence analysis indicated that the results of combined therapy by lesion report were reliable and conclusive. However, in the patient report trials, the frequency of lesions on the hand and foot was higher, and the effect of combined therapy was still non-significant. The authors concluded that calcineurin inhibitors showed a better therapeutic effect than placebo in the treatment of vitiligo with phototherapy. However, the typical UV-resistant sites (i.e., hand and foot) were still difficult to cure even with combined therapy. Moreover, they stated that because of concerns about photo-carcinogenesis, the clinical application of combined therapy should be explored with caution.


## **Gene Polymorphisms Testing for Early Detection of Vitiligo**

Lu and co-workers (2014) evaluated the association of the catalase (CAT) 389 C/T polymorphism with susceptibility to vitiligo. These investigators undertook a literature search and included the relevant studies passing the selection criteria. After the relevant data were extracted from each study, they statistically analyzed the strength of association between the CAT gene and vitiligo risk. A total of 7 relevant studies were identified, comprising 1,531 patients with vitiligo and 1,608 controls. The genotype distribution in the controls of all studies complied with Hardy-Weinberg equilibrium. After pooling all studies, the results indicated that the 389 C/T polymorphisms in CAT were not associated with the risk of vitiligo in Asians and Turks; however the CT genotype might be a genetic risk factor for susceptibility to vitiligo (odds ratio (OR) = 1.77, 95 % CI: 1.30 to 2.43,  $p < 0.001$ ) and the CC genotype might decrease the risk of vitiligo (OR = 0.63, 95 % CI: 0.47 to 0.86,  $p < 0.01$ ) in western Europeans. The authors concluded that the 389 C/T polymorphisms in the CAT gene may be associated with vitiligo in western Europeans. They stated that further studies with larger sample sizes are needed to confirm these findings.

He and associates (2015) noted that the CAT T/C at codon 389 in the exon 9 polymorphism has been implicated in susceptibility to vitiligo but a large number of studies have reported inconclusive results. These researchers assessed the association between the catalase gene polymorphism (389C>T) and the risk of vitiligo. These investigators performed a meta-analysis to analyze the association between 389C>T and vitiligo risk. A total of 8 case-control studies with 2,923 cases and 4,237 controls were included in the meta-analysis. The results indicated that there was no association between this polymorphism and vitiligo (TT + CT versus CC: OR = 1.08, 95 % CI: 0.98 to 1.20,  $p = 0.11$ , T versus C: OR = 1.07, 95 % CI: 0.99 to 1.16,  $p = 0.092$ ). In a subgroup analysis by ethnicity, no significant association between the CAT gene 389C>T polymorphism and vitiligo susceptibility was found in Caucasians (TT + CT versus CC: OR = 1.15, 95% CI = 0.98-1.35,  $P = 0.08$ ; T versus C: OR = 1.07, 95% CI = 0.97-1.19,  $P = 0.173$ ) and Asians (TT + CT versus CC: OR = 1.12, 95 % CI: 0.93 to 1.34,  $p = 0.23$ ; T versus C: OR = 1.07, 95 % CI: 0.94 to 1.21,  $p = 0.321$ ). The authors concluded that these findings suggested that 389C>T may not contribute to vitiligo susceptibility. However, larger primary studies with the consideration of gene-environment and gene-gene interactions are still needed to further evaluate the interaction of CAT gene polymorphism with vitiligo susceptibility.

In a meta-analysis, Li and colleagues (2015) evaluated the association between 2 common polymorphisms (ApaI and BsmI) in the VDR gene and the susceptibility to vitiligo. The PubMed, Cochrane Library and China National Knowledge Infrastructure (CNKI) databases were searched; and OR with 95 % CI was calculated. The strength of association and vitiligo risk was assessed under 5 genetic models:

I. allele,

 **A** dominant,  
III. recessive,  
IV. homozygous, and  
V. heterozygous.

I. allele,  
II. dominant,  
III. recessive,  
IV. homozygous, and  
V. heterozygous.

I. allele,  
II. dominant,  
III. recessive,  
IV. homozygous, and  
V. heterozygous.


A total of 6 relevant studies were identified, including 5 studies that assessed the ApaI polymorphism and 4 the BsmI polymorphism (some overlapped). The meta-analysis results indicated that either the ApaI or the BsmI gene polymorphism may increase the risk of vitiligo in East Asian populations (aa + Aa versus AA: OR = 1.40, 95 % CI: 1.01 to 1.96,  $p < 0.05$ ; bb versus Bb + BB: OR = 1.32, 95 % CI: 1.09 to 1.59,  $p < 0.01$ ). No publication bias was detected in this meta-analysis. The authors concluded that the current meta-analysis suggested that the ApaI a allele or BsmI bb genotype are associated with the risk of vitiligo in East Asian populations. Thus, these polymorphisms could be potential biomarkers for early detection of vitiligo.

## **Cytotoxic T-Lymphocyte Antigen (CTLA)-4+49A/G Polymorphism Testing**

Liang et al (2015) noted that cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a critical negative regulator of T-cell activation and proliferation. Several studies have assessed the association between CTLA-4+49A/G polymorphism and psoriasis and vitiligo, but the results are inconsistent. In a meta-analysis, these researchers examined the association between CTLA-4+49A/G polymorphism and psoriasis and vitiligo susceptibility. The PubMed, Embase, and China National Knowledge Infrastructure (CNKI) databases were searched according to predefined criteria for all relevant studies published prior to July 3, 2014. Odds ratios with 95 % CIs, and heterogeneity and publication bias tests were performed to estimate the strength of the association. A total of 14 studies comprising 6 on psoriasis (700 cases, 781 controls) and 8 on vitiligo (1,514 cases, 2,049 controls) were included. Overall, no significant association was detected between CTLA-4+49A/G polymorphism and psoriasis. There was still no significant relationship when the studies were limited to ethnicity (Asian and Caucasian), HWE or heterogeneity, except the limitation to heterogeneity in the dominant (OR = 0.69, 95 % CI: 0.51 to 0.93,  $I(2) = 0.0\%$ ) and additive (OR = 0.69, 95 % CI: 0.48 to 0.98,  $I(2) = 0.0\%$ ) models, and the limitation to both heterogeneity and HWE in the dominant model (OR = 0.68, 95 % CI: 0.48 to 0.98,  $I(2) = 0.0\%$ ). Both overall and subgroup analyses based on ethnicity, genotype frequencies, and heterogeneity also failed to demonstrate an association between CTLA-4+49A/G polymorphism and vitiligo. The authors concluded that CTLA-4+49A/G polymorphism may not contribute to psoriasis and vitiligo susceptibility, but further well-designed studies with large sample size are needed to confirm this conclusion.

## **TNF-Alpha-308G/A Polymorphism Testing**

Nie and colleagues (2015) noted that several case-control studies have been conducted to investigate the association between the TNF-alpha (TNF- $\alpha$ )-308G/A polymorphism and vitiligo risk. However, the results of these studies are inconsistent; therefore, these researchers attempted to comprehensively evaluate the association between TNF- $\alpha$ -308G/A polymorphism and vitiligo risk via a meta-analysis. Studies reporting the association between TNF- $\alpha$ -308G/A polymorphism and vitiligo risk were retrieved from PubMed and EmBase databases. Data were extracted from these studies and the pooled ORs with 95 % CIs were calculated to assess the

 Association. A total of 6 case-control studies including 1,391 vitiligo cases and 2,455 control subjects were included in this meta-analysis. The overall results showed the lack of a significant difference in TNF- $\alpha$ -308G/A genotype distribution between the patients and controls when the G allele and GG, GG + GA, GG, and GG genotypes were compared against the A allele and the GA + AA, AA, AA, and GA genotypes, respectively (ORs = 0.65, 0.53, 0.63, 0.41, 0.55; 95 % CI: 0.35 to 1.23, 0.24 to 1.18, 0.10 to 4.09, 0.08 to 1.97, 0.25 to 1.21;  $p$  = 0.188, 0.121, 0.627, 0.264, 0.135, respectively). The authors concluded that the findings of this meta-analysis suggested that the TNF- $\alpha$ -308G/A polymorphism may not be associated with vitiligo risk. They stated that as few studies are available in this field and current evidence remains limited, these results must be corroborated with well-designed and larger studies in the future.

## **Human Leukocyte Antigen-A Polymorphism Testing**


Li and colleagues (2016) evaluated the association between vitiligo and human leukocyte antigen- (HLA-) A. Methods. PubMed, Embase, Web of Science, Chinese National Knowledge Infrastructure, and reference lists were searched for relevant original articles. Results. Nineteen case-control studies comprising 3042 patients and 5614 controls were included, in which 33 HLA-A alleles were reported. Overall, three alleles (HLA-A\*02, A\*33, and Aw\*31) were significantly associated with increased risk of vitiligo, two (HLA-A\*09 and Aw\*19) were associated with decreased risk, and the remaining 28 were unassociated. Twelve alleles, seven alleles, and 19 alleles were common to three ethnicities, both types of vitiligo, and both typing methods, respectively. In the subgroup analysis by ethnicity and typing methods, the association of six alleles and five alleles was inconsistent in three populations and both typing methods, respectively. In the subgroup analysis by clinical type, the association of all seven alleles was consistent in both types of vitiligo. Conclusion. The meta-analysis suggests that HLA-A\*02, A\*33, and Aw\*31 are associated with increased risk of vitiligo, while HLA-A\*09 and Aw\*19 are associated with decreased risk of vitiligo. The association of some alleles varies in terms of ethnicity and typing methods.

This study has some limitations. First, the meta-analysis only included published studies. Second, vitiligo may be influenced by not only genetic factors but also environmental factors. The results of the meta-analysis should be interpreted cautiously owing to the lack of available data regarding vitiligo development and its relationship with genetic and environmental factors. Further studies may assess the possible gene-environment interactions in the association. Third, the relatively small samples of some HLA-A alleles limited the statistical power. Finally, we were not able to perform subgroup for each HLA-A allele due to the limited number of eligible studies, which might have affected the results. Therefore, more studies with larger sample sizes focusing on each HLA-A allele are needed to confirm these findings. Despite the limitations listed above, this study still has some strength. To the best of our knowledge, this is the first meta-analysis evaluating the association between vitiligo and a number of HLA-A alleles.

In summary, this meta-analysis suggests that HLA-A\*02, A\*33, and Aw\*31 are associated with increased risk of vitiligo, while HLA-A\*09 and Aw\*19 are associated with decreased risk of vitiligo. Moreover, the association of some alleles varies in terms of ethnicity and typing methods. However, further well-designed studies with larger sample sizes are still needed to confirm our findings.

## **Protein Tyrosine Phosphatase, Non-Receptor Type 22 +1858C→T Polymorphism Testing**

Agarwal and Changotra (2017) stated that protein tyrosine phosphatase, non-receptor type 22 gene, which translates to lymphoid tyrosine phosphatase, is considered to be a susceptibility gene marker associated with several autoimmune diseases. Several studies have demonstrated the association of protein tyrosine phosphatase, non-receptor type 22 +1858C→T polymorphism with vitiligo. However, these studies showed conflicting results. Meta-analysis of the same was conducted earlier that included fewer number of publications in their study. These researchers performed a meta-analysis of a total of 7 studies consisting of 2,094 cases and 3,613 controls to evaluate the possible association of protein tyrosine phosphatase, non-receptor type 22 +1858C>T polymorphism with vitiligo susceptibility. They conducted a literature search in PubMed, Google Scholar and Dogpile for all published paper on protein tyrosine phosphatase, non-receptor type 22 +1858C→T

 polymorphism and vitiligo risk till June 2016. Data analysis was performed by RevMan 5.3 and comprehensive meta-analysis v3.0 software. Meta-analysis showed an overall significant association of protein tyrosine phosphatase, non-receptor type 22 +1858C→T polymorphism with vitiligo in all models (allelic model [T versus C]: OR = 1.50, 95 % CI: 1.32 to 1.71,  $p < 0.001$ ; dominant model [TT + CT versus CC]: OR = 1.61, 95 % CI: 1.16 to 2.24,  $p = 0.004$ ; recessive model [TT versus CT + CC]: OR = 4.82, 95 % CI: 1.11 to 20.92,  $p = 0.04$ ; homozygous model [TT versus CC]: OR = 5.34, 95 % CI: 1.23 to 23.24,  $p = 0.03$ ; co-dominant model [CT versus CC]: OR = 1.52, 95 % CI: 1.09 to 2.13,  $p = 0.01$ ). No publication bias was detected in the funnel plot study. The authors noted that stratifying data by ethnicity showed an association of protein tyrosine phosphatase, non-receptor type 22 +1858C→T with vitiligo in European population (OR = 1.53, 95 % CI: 1.34 to 1.75],  $p < 0.001$ ); but not in Asian population (OR = 0.59, 95 % CI: 0.26 to 1.32,  $p = 0.2$ ). The authors concluded that protein tyrosine phosphatase, non-receptor type 22 +1858 T allele predisposed European individuals to vitiligo. The major drawbacks of this meta-analysis were that as a consequence of ethnic-based studies, these investigators were unable to satisfy data by gender or vitiligo-type.


## **NLRP1 Gene Polymorphisms Testing for Susceptibility to Vitiligo and Associated Autoimmune Diseases**

Li and co-workers (2017) stated that genetic variants are linked to vitiligo and associated autoimmune diseases. In a meta-analysis, these investigators evaluated the effects of the rs12150220, rs2670660, and rs6502867 polymorphisms within the human NLR Family Pyrin Domain Containing 1 (NLRP1) gene. They initially identified 1,306 candidate articles through literature searches of PubMed, WOS, Embase, CNKI, WANFANGI, Ovid, Scopus, and Cochrane in July 2017. After strict screening, these researchers included 19 eligible case-control studies, and analyzed the data using Stata/SE 12.0 software. No difference between vitiligo cases and controls was detected for NLRP1 rs12150220, rs2670660, or rs6502867 under most genetic models [Passociation ( $p$  value of association test)  $> 0.05$ ). With regard to vitiligo-associated autoimmune diseases, like Addison's disease, type 1 diabetes mellitus (T1DM), or systemic lupus erythematosus (SLE), a decreased risk was detected for rs12150220 in the Caucasian subgroup under all models [Passociation  $< 0.05$ , OR  $< 1$ ]. No relationships were observed for other polymorphisms, including rs2670660, rs6502867, and the "A-A, G-T, G-A, A-T" haplotypes of rs2670660/rs12150220 (Passociation  $> 0.05$ ). This meta-analysis demonstrated that within the Caucasian population, the NLRP1 rs12150220 polymorphism may correlate with a decreased risk of vitiligo-associated autoimmune diseases, especially autoimmune Addison's disease, T1DM, or SLE. The authors concluded that they identified a potential genetic relationship in the Caucasian population between the NLRP1 rs12150220 polymorphism and a decreased susceptibility to autoimmune diseases, especially autoimmune Addison's disease, T1DM, or SLE. These autoimmune diseases were all tightly associated with vitiligo. However, these researchers did not observe a strong association between NLRP1 rs12150220, rs2670660, or rs6502867 and vitiligo risk, according to the currently very limited data. Similarly, rs2670660 and rs6502867 polymorphisms and rs2670660/rs12150220 haplotypes (A-A, G-T, G-A, A-T) within NLRP1 appeared to have no effect on the risk of vitiligo-associated autoimmune diseases. They stated that given the fact of insufficient statistical power as stated above, more data are needed to confirm these statements, and further determine the role of NLRP1 SNPs in the presence of vitiligo, or vitiligo together with autoimmune diseases.

## **Blister Roof Grafting**

Janowska and colleagues (2016) stated that vitiligo is a multi-factorial acquired dermatosis characterized by achromic or hypochromic macules and by the absence of functioning melanocytes. Treatment depends on the extent of the affected areas and on disease activity. Surgical techniques have proven to be effective in stable cases but can be time-consuming and, in some cases, aesthetically unsatisfying or painful for the patients. These researchers evaluated the clinical safety and effectiveness of a new automatic epidermal skin harvesting device in patients with stable localized vitiligo over a minimum 12-month period. This new system (CELLUTOME Epidermal Harvesting System, KCI, an ACELITY Company, San Antonio, TX) is a commercially available epidermal skin harvesting system that can be used without local anesthesia or other pre-treatments and has been shown to have low rates of donor site morbidity. Epidermal skin grafts can be used in patients with acute and hard to heal chronic wounds, burns and stable vitiligo. The use of advanced therapies may improve the quality of life,



 Accus benefits and accelerate re-pigmentation of patients with vitiligo. In a pilot study, the authors stated that this system was seen to be a safe and effective means of harvesting epidermal micrografts containing melanocytes for use in patients with stable vitiligo unresponsive to standard therapies.


Cai and associates (2016) stated that epidermal grafting has several advantages over full-thickness or split-thickness grafts in the treatment of complex non-healing wounds. These include the low risk of donor site complications, minimal patient discomfort, and abstention from the operating room. Traditionally, the lack of reliable epidermal harvesting techniques has limited its clinical utilization. The development of an automated suction blister epidermal graft (SBEG) harvesting device may facilitate clinical utilization of this technique. These researchers presented a case series of multi-morbid patients who were poor surgical candidates and were treated with this technique. A retrospective review of all patients treated with CelluTome Epidermal Harvesting System (KCI, an Acelity company, San Antonio, TX) prior to May 2016 at the authors' institution was conducted. A total of 12 patients underwent 14 epidermal grafting procedures. Multiple co-morbidities were identified, including smoking (33 %), immunosuppression by immunotherapy or steroids (25 %), chronic venous insufficiency (25 %), diabetes mellitus (25 %), malignancy (25 %), poly-substance abuse (17 %), HIV/AIDS (17 %), and peripheral artery disease (8 %). Among the 2 acute wounds (less than or equal to 3 months) and 10 chronic wounds, the average wound size was 49.1 cm<sup>2</sup> ( $\pm$  77.6 cm<sup>2</sup>) and the median wound duration was 5.7 months (interquartile range [IQR]: 4.1 to 15.8 months) before SBEG was attempted. These complex wounds had failed prior therapies, such as local wound care (100 %), incision and drainage (58 %), vacuum-assisted closure (33 %), split-thickness skin graft (16 %), and hyperbaric oxygen therapy (8 %). Following the procedure, all donor sites healed within 1 week; 3 patients were lost to follow-up. Of the remaining 9 patients, 4 patients had complete resolution of their wounds at a median follow-up of 13.1 weeks (IQR: 6.8 to 17.3 weeks). Among those with partial resolutions, the average wound size was 4.2 cm<sup>2</sup> ( $\pm$  2.1 cm<sup>2</sup>) with an average wound reduction of 79 % ( $\pm$  23 %). No donor or recipient site complications were observed. The authors concluded that the automated SBEG harvesting device was a safe and effective option for treating complex non-healing wounds in multi-morbid patients who may be poor surgical candidates.

The main drawback of this study was selection bias associated with the retrospective design. These investigators stated that in dealing with complex wounds, patient selection is an integral component of a successful outcome; patients with co-morbidities not suitable for the operating room, wound healing issues, and compliance concerns are poor candidates for traditional skin grafts. The autologous epidermal grafts effectively circumvent these problems and present an attractive alternative. The creation of an automated SBEG harvesting technique further simplified the procedure and minimized post-operative complications. The authors concluded that although this study has shown success in a variety of patients, identification of the ideal patient population may be of interest in follow-up studies.

Krishna and colleagues (2016) stated that vitiligo is a common pigmentary disorder of the skin with a great amount of social stigma attached to it. Although various medical modalities are available for the treatment of stable vitiligo, surgical modality remains the treatment of choice for stable and localized vitiligo. The surgical options range from simple punch grafting to the recent epidermal harvesting methods using a negative pressure unit. Although successful use of multiple methods of epidermal grafting has been reported, most of them are cumbersome and time-consuming. These researchers noted that new automated epidermal harvesting system now commercially available involves a tool that applies both heat and suction concurrently to normal skin to induce epidermal micrografts; it serves as a safe, quick and cost-effective method without anesthesia, with a very minimal downtime for healing and requires an optimal expertise. The duration of re-pigmentation appeared to be faster and more uniform compared to other procedures. The authors concluded that more controlled studies are needed to prove the effectiveness of negative pressure epidermal harvesting in patients with stable vitiligo.

## **Prostaglandins for the Treatment of Vitiligo**

An UpToDate review on "Vitiligo: Management and prognosis" (Grimes, 2017) lists afamelanotide (a potent and longer-lasting synthetic analog of naturally occurring alpha-melanocyte-stimulating hormone), prostaglandin E<sub>2</sub>, and bimatoprost (a synthetic analog of prostaglandin F<sub>2</sub>-alpha) as experimental therapies.

 Aotran and colleagues (2017) stated that latanoprost (LT) is a prostaglandin F2-alpha analog that can induce skin pigmentation, a side effect discovered via its use in the treatment of glaucoma. It up-regulates tyrosinase and promotes melanocyte proliferation. A recent 22-patient, randomized, placebo-controlled trial comparing topical LT to NB-UVB and to the combination of the two, reported that the LT and NB-UVB combination was superior to NB-UVB therapy alone (62.5 versus 12.5 % with greater than 50 % re-pigmentation at 6 months,  $p < 0.05$ ). Latanoprost alone yielded comparable results to NB-UVB (42.9 versus 28.6 % with greater than 50 % re-pigmentation at 6 months,  $p > 0.05$ ) and superior outcomes to placebo (42.9 versus 0 % with greater than 50 % re-pigmentation at 6 months,  $p < 0.05$ ). A Korean case series reported 3 patients with periorbital vitiligo who experienced 20, 50, and greater than 90 % re-pigmentation after 2 months of topical LT therapy. Likewise, a phase IV clinical trial in India investigating topical bimatoprost 0.03 % solution twice-daily observed 50 to 100 % re-pigmentation in 7 of 10 patients after 4 months. Results were first visible at 2 months, and patients with recalcitrant, focal vitiligo as well as those with disease duration less than 6 months tended to respond best. The authors stated that these promising results clearly warrant further investigation into LT's safety and effectiveness for the treatment of vitiligo.

Jha and colleagues (2018) evaluated the efficacy of topical bimatoprost ophthalmic solution in stable facial vitiligo. A total of 8 cases of stable facial vitiligo were treated with bimatoprost 0.03 % ophthalmic solution once-daily for 12 weeks. Photographic records were taken at 2 weeks follow-up along with dermoscopic (Polarized, 10 $\times$ ) evaluation; 4 cases had excellent re-pigmentation, 2 cases had partial re-pigmentation and 2 cases had poor response. The authors concluded that bimatoprost appeared to be promising in treating stable vitiligo; but large-scale studies are needed.


## **Apremilast**

Huff and Gottwald (2017) stated that psoriasis, alopecia areata, and vitiligo share a common pathway of autoimmunity, inflammatory signals, and cytokines present, although their pathogenesis is not completely understood. Apremilast is FDA-approved for psoriasis and psoriatic arthritis; it has also been shown to inhibit the development of alopecia areata. These researchers presented the case of a 52-year old woman with vitiligo for over 2 decades, and demonstrated the ability of apremilast to allow for re-pigmentation in this patient with chronic recalcitrant vitiligo in conjunction with initial systemic glucocorticoids. Moreover, they stated that additional clinical studies, ideally a randomized placebo-controlled trial, would be needed to prove that apremilast leads to re-pigmentation in vitiligo.

## **Topical Phenytoin Gel**

Abdou and associates (2017) noted that there are many theories explaining vitiligo such as genetic, autoimmune, neural, free radicals, biochemical, intrinsic defect, melanocytorrhagy, and convergent theories. Phenytoin is a widely used anti-convulsant, which is used in cutaneous medicine for treatment of ulcers and epidermolysis bullosa. These researchers evaluated the effectiveness of topical phenytoin gel in the treatment of vitiligo patients and explaining the underlying mechanism using immunohistochemistry for evaluation of HMB45, CD4, and CD8. Only 9 patients out of 28 experienced response to phenytoin in the form of dull, white color change and light brown color. Post-phenytoin treatment biopsies showed decreased density of inflammation, increased melanin and increased HMB45 positive cells together with an increased number of CD4-positive lymphocytes and decreased number of CD8-positive lymphocytes. These observations did not reach significant level ( $p > 0.05$ ). A high percentage of CD4-positive lymphocytes was significantly associated with a long duration of vitiligo ( $p = 0.03$ ) and segmental vitiligo type ( $p = 0.02$ ). The current study applied phenytoin as 2 % concentrated gel for 3 months, which was a relatively short duration without observed side effects throughout the period. The authors concluded that these findings indicated that topical phenytoin of low concentrations may have beneficial effects through immunomodulatory activity by affecting CD4 and CD8 counts and subsequently the ratio between them. They stated that further studies are recommended to combine phenytoin with other anti-vitiligo agents such as local corticosteroids or phototherapy to clarify if it could potentiate their effects.

## **Unconventional Treatments for Vitiligo**


 Gianfaldoni and colleagues (2018a) stated that despite the numerous therapies of proven efficacy available for vitiligo treatment, new unconventional drugs had been introduced for the correction of cutaneous disease in the last decades.

Capecitabine is an oral prodrug of fluorouracil, used in the treatment of metastatic colon and breast cancers. It has been reported that its use cause cutaneous hyperpigmentation. At the moment, more studies are needed to evaluate the potential use of the drug in the treatment of vitiligo.

- Glutathione is a well-known antioxidant able to protect cellular components by oxidative stress damage. Recently, some studies underlined how its oral use as supplement may be useful in preventing cells photo-damage. However, the authors stated that more data are needed for its potential use in the treatment of vitiligo.
- Melagenine is an alcohol extract of human placenta, which has been proposed for the topical treatment of vitiligo patients. Even if the exact mechanism of action is still unclear, it appeared to stimulate the melanoblast and melanocyte proliferation and the melanogenesis. It is usually applied twice-daily, alone or in association with ultraviolet radiation. Interestingly, a pilot study underlined the effectiveness of topical melagenine in combination with 20 minutes of infrared exposure twice-daily, in the re-pigmentation of scalp vitiligo. Recently a new formulation of melagenine (Melagenina plus) has been formulated; it consists of a alcohol human placental extract with calcium. The drug is applied once-daily, and appeared to be effective in stimulating the re-pigmentation. No side effects had been described in the use of both Melagenine and Melagenine plus. However, no recent data are available on the use of melagenine in vitiligo.
- Tars are oily, viscous material, consisting mainly of hydrocarbons, produced by the destructive distillation of organic substances such as wood, coal, or peat. Previously, they had been used for the topical treatment of psoriasis, both alone or in association to UVR. Because of their anti-inflammatory and immunosuppressive effects, tars had been also proposed for the treatment of vitiligo. However, they are not used, not only because of the limited data on their effectiveness, but also for their toxicity and carcinogenic effects.
- Topical minoxidil (2 % or 5 %) is a vasodilator drug, which is used topically to treat different forms of hair loss (e.g., male androgenetic alopecia, female androgenetic alopecia, alopecia areata and other). Even if exact mechanism of action is not well understood, it appeared possible that, by widening blood vessels, minoxidil allows more oxygen and nutrients to the hair follicles. Regarding its potential use in vitiligo treatment, only the study of Srinivas et al. reported its efficacy. The authors described how the association of the daily use of topical 2 % minoxidil with alternate day PUVA, was able to induce local hypertrichosis and marker re-pigmentation in 2 vitiligo patients. Unfortunately, no other studies about minoxidil in vitiligo have been conducted and some clinical reports described controversial results, such as the appearance of leucoderma after the use of the drug.
- Topical cream containing pseudocatalase has been proposed as a therapeutic tool for vitiligo. The drug acts by reducing the free radicals and improving the catalase action. Generally, it is applied twice-daily. Better results appeared to be achieved when pseudocatalase is associated to sol-therapy, UVA or nb-UVB. However, not all the research confirmed these data: some studies described how the use of pseudocatalase, alone or in association with UVR, did not add any benefits.

Gianfaldoni and colleagues (2018b) noted that Neovir is an intramuscular Immunomodulatory agent, composed of sodium oxo – dihydro – acridinyl - acetate (ODHAA). It is usually used to normalize impaired immune system functions under various conditions, such as viral infections, immunodeficiency, oncological diseases and multiple sclerosis. An experimental study evaluated the efficiency of acridone acetic acid, sodium salt, in stopping active non-segmental vitiligo progression. A total of 60 patients with active non-segmental vitiligo were treated with ten intramuscular injections, every 48 hours, of ODHAA. Vitiligo progression was assessed in 1, 3, 6 and 12 months after treatment. The results of the preliminary study were excellent: sodium oxodihydroacridinylacetate showed high efficiency in achieving long-term stabilization of non-segmental vitiligo. These preliminary findings need to be validated by well-designed studies.

## **Carbon Dioxide Fractional Laser**

 Academia colleagues (2018) noted that tacrolimus is a conventional medication for the treatment of vitiligo, but the effect of a single medication is limited. These researchers examined the effects, adverse responses, and re-pigmentation results of the joint treatment of vitiligo by carbon dioxide (CO<sub>2</sub>) fractional laser together with tacrolimus. A total of 45 patients with vitiligo were randomly divided into 2 groups: Treatment (T) group and control (C) group, and each group was further divided into 3 subgroups (face, torso and limbs, and hand and foot) according to the location of the skin defect. Both groups used topical 0.1 % tacrolimus cream, but the T group was given 1 CO<sub>2</sub> fractional laser treatment each month. These investigators evaluated the clinical efficacy, adverse responses, and re-pigmentation results after 6 months. Compared to the C group, the T group showed better improvement in both objective and subjective assessments. When the treatment time was increased, the efficacy was also improved, and the re-pigmentation in the T group occurred in 3 ways: peri-follicular re-pigmentation, marginal re-pigmentation as well as diffuse re-pigmentation. There were 3 cases of isomorphic responses (2 cases in the rapid progression stage, 1 case in the progression stage), and 1 case formed scarring on the neck in the T group. The authors concluded that the treatment of vitiligo by CO<sub>2</sub> fractional laser together with tacrolimus was effective and was most suitable for patients in the progression stage. Patients in the rapid progression stage should use this approach with caution, and its efficacy was limited for patients in the stable stage. An extended course of treatment was helpful for the re-pigmentation of white patches. All 3 forms of re-pigmentation could occur in the joint treatment of vitiligo by CO<sub>2</sub> fractional laser together with tacrolimus. These preliminary findings need to be validated by well-designed studies.

Chiu and associates (2018) stated that the treatment of stable non-segmental vitiligo is often challenging, which new therapies are being searched. Multiple clinical trials have proposed the benefits and safety of using fractional CO<sub>2</sub> laser as an adjunct therapy to conventional treatments. These researchers examined the safety and efficacy of fractional CO<sub>2</sub> laser as a combination therapy to conventional treatments in patients with stable non-segmental vitiligo. They carried out a literature search using PubMed, Embase, and the Cochrane Library for comparative studies among vitiligo patients treated with additional fractional CO<sub>2</sub> laser. Clinical outcomes in the selected studies were compared, and a meta-analysis was performed via Review Manager version 5.3, according to the PRISMA guidelines. A total of 6 studies with 184 patches/patients were included in this meta-analysis. The combination therapy group had significantly superior results than that of the control group (greater than or equal to 75 % re-pigmentation, RR 2.80, 95 % CI: 1.29 to 6.07; greater than or equal to 50 % re-pigmentation, RR 2.26, 95 % CI: 1.23 to 5.9; less than 25 % re-pigmentation, RR 0.57, 95 % CI: 0.43 to 0.75). the authors concluded that the findings of this meta-analysis showed that using fractional CO<sub>2</sub> laser in combination with conventional treatments was safe and efficient, and may be considered as an adjunct therapeutic option for patients with refractive non-segmental vitiligo. Moreover, these researchers stated that the drawbacks of this study included the small number of studies (n = 6) and sample size (total of 184 patches/patients), inadequate blinding of subjects, as well as variation between therapy protocols.

Furthermore, an UpToDate review on “Vitiligo: Management and prognosis” (Grimes, 2019) does not mention carbon dioxide fractional laser as a therapeutic option.

## **Interleukins for the Treatment of Vitiligo**

Gomes and colleagues (2018) note that there is few summarized information regarding the role of inflammatory mediators, such as interleukins (ILs), in vitiligo. These investigators performed a systematic review of the role of interleukins in vitiligo. They included all studies assessing IL levels in vitiligo patients conducted up to June 2017. Quality assessment of these studies was performed using the Newcastle-Ottawa Scale (NOS). The ILs mainly involved were IL-2, IL-4, IL-6, IL-10 and IL-17. The studies highlight the crucial role of IL-17 in the onset and progression of the disease, and its synergistic action with IL-2, IL-6 and IL-33. Dysregulated levels of the ILs were also correlated with the stage of disease, the affected skin surface area, and indicated as the main factor for lymphocyte infiltration found in depigmented regions. The authors concluded that these findings showed the growing need for new therapies targeting vitiligo and further research on the role of ILs as a treatment is needed.

Furthermore, an UpToDate review on “Vitiligo: Management and prognosis” (Grimes, 2019) does not mention interleukins as a therapeutic option.



## Apremilast in Combination with Narrowband Ultraviolet B for the Treatment of Vitiligo

Khemis and colleagues (2020) noted that scientific rationale and encouraging first clinical results suggested the interest of using apremilast for treating vitiligo. In a 52-week, prospective, randomized, placebo-controlled study, these researchers compared the efficacy of apremilast in combination therapy with narrow-band ultraviolet B (NB-UVB) versus placebo and NB-UVB treatment for re-pigmentation in patients with non-segmental vitiligo. Group A received, in addition to phototherapy, apremilast at the label dosage, and group B received placebo. After 24 weeks, patients who responded (decreased Vitiligo Area Scoring Index [VASI] of greater than 30 %) were re-randomized to receive apremilast or placebo, combined with twice-weekly NB-UVB for 24 additional weeks. The primary outcome measure was the comparison between the 2 groups of the VASI score at 24 weeks. A total of 80 patients were randomized (40 in each group). After 24 weeks, the mean VASI score decreased from 23.63 to 19.49 ( $p = 0.011$ ) in the apremilast + UVB group and from 21.57 to 15.25 ( $p < 0.0001$ ) in the placebo + UVB group. The difference between the 2 groups was not statistically significant ( $p = 0.18$ ).

No statistically significant differences were observed between the 2 groups after an additional 24 weeks of treatment. The authors concluded that apremilast did not bring any benefit to NB-UVB in the treatment of vitiligo.

## Methylenetetrahydrofolate Reductase (MTHFR) Gene and Cystathionine B Synthase (CBS) Gene Polymorphisms

Jadeja and co-workers (2018) noted that several studies have reported hyper-homocysteinemia in vitiligo patients, suggesting the potential role of elevated homocysteine (Hcy) levels in precipitating vitiligo. These researchers estimated Hcy and vitamin B12 levels, and examined the role of MTHFR 677 C > T and 1298 A > C polymorphisms in vitiligo susceptibility in Gujarat population; Hcy and vitamin B12 levels were estimated in plasma of 55 vitiligo patients and 60 controls by electrochemiluminescence immunoassay (ECLIA). Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) techniques were used to genotype MTHFR 677 C > T and 1298 A > C polymorphisms in 520 vitiligo patients and 558 controls. The results showed significantly elevated Hcy levels ( $p = 0.0003$ ) as well as significant decrease in vitamin B12 levels ( $p = 0.0102$ ) in vitiligo patients, as compared to controls. No significant difference in genotype and allele frequencies of MTHFR 677 C > T polymorphism was observed among patients and controls, however, the frequency of 'CC' genotype of MTHFR 1298 A > C polymorphism was significantly increased in patients as compared to controls ( $p = 0.0151$ ). Analysis based on the type of vitiligo revealed a significant increase in 'C' allele of MTHFR 1298 A > C polymorphism in patients with generalized ( $p = 0.003$ ) and active ( $p = 0.007$ ) vitiligo as compared to controls. Both the polymorphisms of MTHFR were in low linkage disequilibrium (LD) and susceptible 'TC' haplotype was more frequently observed ( $p = 0.008$ ) in vitiligo patients. Interestingly, elevated Hcy levels were also positively correlated with MTHFR 1298 A > C polymorphism in vitiligo patients. Structure based in silico prediction revealed structural perturbations in MTHFR protein due to Ala222Val and Glu429Ala amino acid substitution. The authors concluded that the findings of this study suggested a possible role of altered Hcy and vitamin B12 levels in precipitation and progression of vitiligo in genetically susceptible individuals. Interestingly, MTHFR 1298 A > C polymorphism was found to be associated with autoimmune vitiligo. Correlating MTHFR polymorphisms with its enzyme activity in patients and controls would be interesting and further studies in this direction will shed light on the role of Hcy in melanocyte biology and vitiligo pathogenesis.

El Tahlawi and colleagues (2020) noted that an elevated Hcy level has been described in vitiligo.

Methylenetetrahydrofolate reductase (MTHFR) and cystathionine B synthase (CBS) are major determinants of the homocysteine metabolism. These researchers examined serum Hcy levels in vitiligo patients as well as the association between MTHFR (C677T, A1298C) and CBS gene polymorphisms and susceptibility to vitiligo in a sample of those populations; Hcy levels were estimated by radioimmunoassay while MTHFR (C677T, A1298C) and CBS gene polymorphisms were detected by the PCR-RFLP technique in 100 vitiligo patients and 80 healthy controls. The Hcy level was significantly higher in vitiligo patients than controls ( $p = 0.000$ ). Significant differences in the genotype and allele distributions of single nucleotide polymorphisms (SNPs) of the MTHFR (C677T, A1298C) with the mutant genotypes were more common in the controls than patients ( $p = 0.001, 0.029$ ,

actively); CBS gene mutant genotypes and alleles were more common in vitiligo patients than controls ( $p = 0.002$ ). The authors concluded that CBS and MTHFR gene polymorphisms may play a major role in the genetic susceptibility to vitiligo.

Chang and associates (2020) stated that MTHFR is an important enzyme that converts 5,10-methylenetetrahydrofolate into 5-methylenetetrahydrofolate, which provides the methyl group to convert Hcy to methionine. Two common MTHFR gene polymorphisms, C677T (rs1801133) and A1298C (rs1801131), are associated with decreased MTHFR enzyme activity, and several studies have reported the involvement of these polymorphisms in susceptibility to diseases, including autoimmune diseases. Vitiligo is a common cutaneous hypo-pigmentation disease resulting from the loss of functional melanocytes due to autoreactive CD8<sup>+</sup> T cells or oxidative stress in genetically predisposed individuals. Available studies have reported inconsistent results regarding the relationship between MTHFR polymorphisms and vitiligo; thus, these investigators evaluated this topic in a systematic review and meta-analysis. They carried out a systematic search of PubMed, Embase, Cochrane Library, and Web of Science for case-control studies published before December 9, 2019 that compared the expression of MTHFR polymorphisms in patients with vitiligo and healthy controls. The keywords were “methylenetetrahydrofolate reductase” or “MTHFR” combined with “vitiligo”. Study quality was assessed using the Newcastle-Ottawa Scale. A random effects model was employed for pooled analysis. Heterogeneity across studies was assessed using the I<sup>2</sup> statistic, and the risk of publication bias was assessed using Egger’s test; ORs and 95 % CIs were utilized as summary statistics and were calculated using Comprehensive Meta-Analysis Version 3 (Biostat, Inc., Englewood, NJ). A  $p$ -value of  $< 0.05$  was considered statistically significant. A total of 25 relevant studies were initially identified, most of which were sequentially excluded because they were duplicates, concerned an unrelated topic, or were a review. A final total of 5 case-control studies, which had recruited 1,703 patients with vitiligo and 1,708 controls, were included in the meta-analysis. Pooled analysis of 5 included studies revealed no difference in the prevalence of MTHFR C677T gene polymorphisms in patients with vitiligo from that in controls, and meta-analyses of the prevalence of MTHFR A1298C gene polymorphisms also showed no significant difference between patients with vitiligo and controls. High heterogeneity across the studies was found for all analyses. No publication bias was detected in any measurement. The authors concluded that this meta-analysis demonstrated no significant association between MTHFR C677T or A1298C gene polymorphisms and the risk of vitiligo. Moreover, these researchers stated that the drawbacks of this analysis included the lack of information for other MTHFR polymorphism variants and insufficient data on different ethnicities or vitiligo subtypes.

## **Intradermal Mesotherapy (Injections of Bio-revitalizant NCTF135) for the Treatment of Vitiligo**

In a pilot study ( $n = 7$ ), Konstantinova and colleagues (2019) evaluated a novel treatment for vitiligo. These researchers injected skin affected with vitiligo intra-dermally with a complex of vitamins and minerals and assessed the outcome; subjects having been diagnosed with generalized progressive vitiligo. In all cases, multiple therapies had been previously attempted. All patients were subjected to intradermal injections of bio-revitalizant NCTF 135 (3 mls) in the hypo-pigmented areas of skin, once-weekly for 5 weeks. A 30-G x 13-mm needle was used for the 0.025-ml intradermal injections to create micro-papules with a 1-cm distance between the injection sites. The results were assessed at 2 weeks and 5 weeks and were considered successful if partial or complete re-pigmentation was achieved. Partial or complete skin re-pigmentation post-treatment was observed in vitiligo macules of all patients (100 %). No significant side effects, or exacerbation of vitiligo were observed during or after treatment with NCTF 135 in the following 6 months (5 patients) and 12 months (2 patients). The authors concluded that increasing the armamentarium of new treatments of vitiligo is important. Previous studies showed the effectiveness of oral and intramuscularly injected multi-vitamins in the treatment of vitiligo, explaining the results by the antioxidative qualities of the above. The findings of this pilot study demonstrated that intradermal mesotherapy injections of NCTF135, rich with vitamins and other antioxidants were well-tolerated and effective in achieving significant re-pigmentation of de-pigmented skin in all patients studied, including 5 who had been resistant to previous standard therapies. These preliminary findings need to be validated by well-designed, controlled studies.


## Assurement of Interleukin-17 (IL-17) Level for the Management of Vitiligo

Acharya and Mathur (2020) stated that the role of the pro-inflammatory cytokine, interleukin-17 (IL-17) is being continuously explored in various autoimmune disorders. Studies have assessed the levels of IL-17 in vitiligo patients. In a systematic review and meta-analysis, these researchers examined the IL-17 levels in vitiligo patients in comparison with the healthy controls. They carried out a systematic review of the existing literature in PubMed, Scopus and Cochrane databases. The data needed to calculate the pooled effect size in the form of standardized mean difference (SMD) with the corresponding 95 % CI were extracted from the eligible studies. Separate analyses for active and stable vitiligo were also performed. A total of 11 case-control studies with 626 vitiligo patients and 475 healthy controls were included. Random-effects meta-analysis found significantly higher serum IL-17 levels in vitiligo patients compared with the healthy controls (SMD = 1.67, 95 % CI: 1.11 to 2.22,  $p < 0.001$ ). The IL-17 levels were higher in both active (SMD = 1.31, 95 % CI: 0.76 to 1.86) and stable (SMD = 1.47, 95 % CI: 0.59 to 2.35) vitiligo patients compared with the healthy controls. The skin IL-17 levels were also significantly higher in vitiligo patients (SMD = 1.28, 95 % CI: 0.82 to 1.74). The authors concluded that the findings of this meta-analysis suggested that vitiligo patients had significantly elevated IL-17 levels. These researchers stated that further examination of this association could have implications for the treatment of vitiligo. They noted that heterogeneity in the baseline characteristics of the included studies was the major drawback of this study.

### Fire Needle Therapy (Acupuncture)

Luo and colleagues (2020) stated that fire needle therapy (method of rapid piercing of acupoints with red-hot needles) has been reported as an effective treatment for vitiligo; however, current clinical evidence has not been systematically evaluated. In a systematic review, these researchers examined if fire needle therapy is safe and effective for the treatment of vitiligo. A total of 7 databases were searched until October 2019 for RCTs on fire needle therapy, with and without conventional treatments, versus any type of conventional therapy for treating vitiligo. The RevMan 5.3.5 software was used to perform meta-analysis of the included studies. A total of 47 trials comprising 3,618 patients were included. Fire needle combined with conventional vitiligo treatments had a higher efficacy (RR: 1.55, 95 % CI: 1.46 to 1.65,  $p < 0.00001$  and RR: 1.41, 95 % CI: 1.24 to 1.61,  $p < 0.00001$ , respectively) and a greater effect on restoring the color of the area of the skin lesion (mean difference (MD): 3.40, 95 % CI: 2.11 to 4.69,  $p < 0.00001$ ), increasing the pigment point of vitiligo (MD: 0.83, 95 % CI: 0.54 to 1.13,  $p < 0.00001$ ) and improving the cytokine level (MD: 8.10, 95 % CI: 6.94 to 9.27,  $p < 0.00001$ ) and effectual time (MD: -4.76, 95 % CI: -7.33 to -2.19,  $p = 0.0003$ ) than traditional methods. Limb lesions (RR: 1.60, 95 % CI: 1.31 to 1.95,  $p < 0.00001$ ) were more effectively treated when the treatments included fire needles, whereas the therapeutic effect of fire needles on either the head and neck (RR: 1.13, 95 % CI: 0.78 to 1.64,  $p = 0.52$ ) or torso lesions (RR: 1.22, 95 % CI: 0.82 to 1.81,  $p = 0.33$ ) was not significantly different compared to that without fire needles. No statistically significant differences in adverse effects (RR: 1.15, 95 % CI: 0.89 to 1.49,  $p = 0.28$ ) and recurrence rates (RR: 0.90, 95 % CI: 0.17 to 4.92,  $p = 0.91$ ) during the follow-up period were observed between treatment with and without fire needles. The authors concluded that fire needle therapy combined with other conventional treatments was useful in treating vitiligo. These researchers stated that results of this systematic review showed that there is still a lack of well-designed studies on fire needle therapy in the treatment of vitiligo. They stated that further high-quality studies with larger sample sizes are needed to make a conclusive judgment.

The authors stated that this study had several drawbacks. The studies included in this review generally had poor methodologies, which could have caused bias. Not all studies mentioned the method of random order generation. Furthermore, only 2 trials mentioned the blinding method and 1 trial utilized concealment of allocation. Moreover, the difficulties associated with blinding in studies of acupuncture treatment led to a low methodological quality, causing possible selection bias in RCTs. The safety and efficacy of acupuncture treatment is attracting increasing attention from the domestic and international medical communities. Nevertheless, acupuncture, particularly fire needle therapy, differed significantly in characteristics from drug treatment; therefore, effective blinding and the selection of an appropriate placebo had long been recognized as extremely challenging. It was quite clear that the development of more appropriate RCT designs and protocols was an urgent problem that acupuncture therapy faced. Since fire needle therapy was a traditional Chinese

 treatment, all of the studies included were performed in China. The therapy's application in other countries and regions must be studied further. Few studies mentioned the recurrence of lesions and the efficacy of the treatment for lesions placed at different locations, which might have brought about a difference in the results. In addition, most existing studies had small sample sizes, which might have produced a high level of bias.


## **Oral Mini-Pulse Therapy Plus Narrow-Band Ultraviolet B**

Lee and associates (2016) noted that systemic corticosteroids have been used to arrest the progression of vitiligo; however, side effects have been a constant issue. In a retrospective study, these researchers examined the efficacy and side effect of oral mini-pulse (OMP) therapy with methylprednisolone (MPD) combined with narrow-band ultraviolet B (NB-UVB) for adults with non-segmental vitiligo. A total of 32 patients with extensive and/or spreading vitiligo received 0.5 mg/kg MPD on 2 consecutive days per week with NB-UVB therapy for at least 3 months. All subjects (100 %) showed progression arrest within 12 weeks; 19 out of 32 patients (59.4 %) exhibited re-pigmentation on more than 25 % of lesions; 13 patients (40.6 %) attained satisfactory re-pigmentation in more than 50 % of lesions. Only 2 patients discontinued the medication due to gastro-intestinal (GI) trouble. The authors concluded that OMP therapy with MPD combined with NB-UVB appeared effective in arresting vitiligo progression and rapidly inducing re-pigmentation with minimal side effects. This was a retrospective study with a relatively small ( $n = 32$ ) sample size, and short-term follow-up (12 weeks); its findings need to be validated by well-designed studies with larger sample sizes and longer follow-up.

Dellatorre and co-workers (2020) noted that the prevalence of vitiligo in Brazil was determined to be 0.54 %. There is no on-label medication for its treatment. To-date, no Brazilian consensus on the treatment of vitiligo had been written. The objective of this group of Brazilian dermatologists with experience in the treatment of vitiligo was to reach a consensus on the clinical and surgical treatment of this disease, based on articles with the best scientific evidence. A total of 7 dermatologists were invited, and each was assigned 2 treatment modalities to review. Each treatment (topical, systemic, and phototherapy) was reviewed by 3 experts; 2 experts reviewed the surgical treatment. Subsequently, the coordinator compiled the different versions and drafted a text regarding each type of treatment. The new version was returned to all experts, who expressed their opinions and made suggestions for clarity. The final text was written by the coordinator and sent to all participants to prepare for the final consensus. The experts defined the following as standard treatments of vitiligo: the use of topical corticosteroids and calcineurin inhibitors for localized and unstable cases; corticosteroid mini-pulse in progressive generalized vitiligo; NB-UVB for extensive forms of the disease. Surgical modalities are indicated for segmental and stable generalized vitiligo. Topical and systemic anti-JAK drugs are being tested, with promising results. Moreover, these researchers stated that the OMP regimen can be combined with phototherapy in patients with progressive vitiligo, although controlled studies with long-term follow-up are still needed.

Chavez-Alvarez and colleagues (2021) stated that there is limited evidence supporting the use of alternative treatments for patients with non-stable vitiligo. In a systematic review, these investigators examined the effects of OMP therapy in the management of non-segmental vitiligo. The following databases were searched between inception and May 2020 for relevant studies: Scopus, Web of Science, Medline, and Embase. All RCTs that compared OMP therapy with any other active treatment or placebo for non-stable vitiligo were included. The Cochrane's risk of bias tool was used to evaluate the risk of bias (ROB) in selected studies, and the overall quality of evidence of each outcome was evaluated using the Grading Recommendations, Assessment, Development, and Evaluations (GRADE) system. A total of 4 studies met selection criteria; all of them were conducted in India and included 246 patients. OMP therapy included betamethasone or dexamethasone. The duration of treatment was 6 months in all studies. Up to 32 % of patients achieved a re-pigmentation rate of greater than 75 % when OMP therapy was administered as monotherapy. No difference was observed between OMP therapy and other treatments in arresting the disease, and weight gain was the most frequent adverse effect. The overall ROB in all included studies was relatively high because of the randomization process, outcome measurement and informed selection of outcomes. The authors concluded that based on the findings of these studies, OMP therapy did not demonstrate additional value compared with other treatments; thus, there is an urgent need to conduct high-quality clinical trials to evaluate this therapy.




 UpToDate review on “Vitiligo: Management and prognosis” (Grimes, 2021) states that “Vitiligo involving 10 to 40 % of the BSA -- For patients with moderate to extensive disease, we suggest phototherapy with NB-UVB rather than PUVA as initial therapy (Grade 2C). NB-UVB phototherapy is administered 2 to 3 times per week for 9 to 12 months or up to 200 treatments. Topical corticosteroids or topical calcineurin inhibitors may be intermittently used in combination with NB-UVB phototherapy”. Oral corticosteroids are not mentioned as a combinational option with NB-UVB.

Furthermore, an UpToDate review on “UVB therapy (broadband and narrowband)” (Honigsmann, 2021) does not mention oral corticosteroids and NB-UVB as a combinational therapy for the treatment of vitiligo.

## Home-Based Phototherapy

Eleftheriadou and colleagues (2014) noted that hand-held NB-UVB units are light-weight devices that may overcome the need to treat vitiligo in hospital-based phototherapy cabinets, allowing early treatment at home that may enhance the likelihood of successful re-pigmentation. The pilot Hi-Light trial examined the feasibility of conducting a large multi-center, randomized controlled trial (RCT) on the use of such devices by exploring recruitment, adherence, acceptability, and patient education. This was a feasibility, double-blind, multi-center, parallel group RCT of hand-held NB-UVB phototherapy for the treatment of vitiligo at home. The overall duration of the trial was 7 months; 3 months recruitment and 4 months treatment. Participants were randomly allocated to active or placebo groups (2:1 ratio). The primary outcome measure was the proportion of eligible participants who were willing to be randomized. The secondary outcomes included proportion of participants expressing interest in the trial and fulfilling eligibility criteria, withdrawal rates and missing data, proportion of participants adhering to and satisfied with the treatment, and incidence of NB-UVB short-term adverse events. A total of 83 % (45/54) of vitiligo patients who expressed interest in the trial were willing to be randomized. Due to time and financial constraints, only 29/45 potential participants were booked to attend a baseline hospital visit. All 29 (100 %) potential participants were confirmed as being eligible and were subsequently randomized. Willingness to participate in the study for General Practice (family physicians) surgeries and hospitals were 40 % and 79 %, respectively; 86 % (25/29) of patients adhered to the treatment and 65 % (7/11) of patients in the active group had some degree of re-pigmentation. Only 1 patient in the active group reported erythema grade 3 (3 %). Both devices (Dermfix 1000 NB-UVB and Waldmann NB-UVB 109) were acceptable to participants. The authors concluded that hand-held NB-UVB devices need evaluation in a large, pragmatic RCT. This pilot trial has explored many of the uncertainties that need to be overcome before embarking on a full scale trial, including the development of a comprehensive training package and treatment protocol. The study has shown strong willingness of participants to be randomized, very good treatment adherence and re-pigmentation rates, and provided evidence of feasibility for a definitive trial. This trial was not intended as an efficacy trial.

Ashraf and colleagues (2022) noted that vitiligo may be treated with hospital-based phototherapy; however, this requires long-term frequent appointments. Self-treatment using home-based phototherapy is a convenient alternative, which may improve adherence and results, but evidence is limited, and so it is not routinely recommended. In a systematic review, these investigators examined the safety and effectiveness of home-based phototherapy for vitiligo. They carried out searches on Medline, Scopus and the Cochrane Library for RCTs comparing home-based phototherapy with institution-based phototherapy or placebo/no phototherapy for vitiligo. The primary outcome was treatment effectiveness. CASP criteria were used for quality assessment. Data were synthesized in a meta-analysis where appropriate. A total of 3 studies (195 subjects) were included: 2 compared home-based with institution-based phototherapy, and 1 compared home-based phototherapy with placebo. Studies were of mixed quality. Therapy regimes varied across studies. Findings on effectiveness were contradictory across studies with variable rates of re-pigmentation. There was no significant difference in re-pigmentation rates between the 2 groups, although adherence to treatment schedules was significantly better in home-based groups. Adverse effects were significantly higher in home-based groups. No long-term data were reported on maintenance of treatment benefits. The authors concluded that although adherence to treatment was significantly better with home-based phototherapy, data were insufficient to form conclusions on effectiveness. These researchers stated that home-based phototherapy had a significantly higher risk of adverse effects, making it difficult to recommend in clinical practice. However, as it offered logistical advantages for patients, its

ness alongside additional safety measures should be examined further in large-scale, good-quality RCTs, with standardized outcome measures, including patient-reported outcomes.


## **Image Analysis Systems for Surface Calculation of Vitiligo Lesions**

Van Geel et al (2022) noted that several digital image analysis systems have been developed for surface calculation of vitiligo lesions. Critical assessment of their measurement properties is crucial to support evidence-based recommendations on the most suitable instruments and will reveal the need for future research. In a systematic review, these investigators examined the measurement properties of digital and analog analysis systems for surface calculation of vitiligo lesions following the Consensus-Based Standards for the Selection of Health Measurement Instruments (COSMIN) recommendations. A total of 19 clinical trials were selected including 25 different instruments. Manual tracing on transparent sheets (contact planimetry) combined with digital measurement or point counting can be considered as the best validated method for the evaluation of target lesions taking into account the skin curvatures. These researchers stated that two-dimensional (2D) digital imaging analysis on photographs also appeared robust although confirmatory data of different research groups using the same digital instrument in a wide range of skin types are missing. Analysis based on 3D photography is still in its early stage but is promising for whole-body analysis. However, the reported data on the quality of the instruments for surface area calculation of vitiligo lesions were in general rather limited. The authors concluded that according to the findings of this systematic review, tracing lesion contours on transparent sheets and digital analysis of photographs based on color segmentation scored favorably for measuring vitiligo target lesions, while supporting data on full-body image analyses is still lacking. Thus, for full body evaluation, clinicians still rely on currently available clinical assessment tool. Contact planimetry (tracing on transparent sheets) can be used as a reference tool for comparison in studies on validation of other measurement instruments as it takes the 3D skin curvatures into account. These researchers noted that a validated full automatic digital analysis system for full-body assessments or target lesions is currently not available. They stated that to complete the assessment of measurement properties of specific instruments, further validation research is needed, preferably by following the COSMIN guidelines, so more higher quality methodological studies can be carried out.


## **Comparison of NB-UVB Combination Therapy Regimens for the Treatment of Vitiligo**

Zhu et al (2023) noted that vitiligo is an autoimmune disease and some guidelines for the management of vitiligo encouraged the use of NB-UVB combination therapies to enhance re-pigmentation. In a systematic review and network meta-analysis, these researchers compared the effectiveness of current NB-UVB combination regimen at the improvement in re-pigmentation. They searched the electronic databases for RCTs related to NB-UVB combination therapy for vitiligo till October 2022; STATA15.0 software was employed to conduct data analysis. A total of 28 eligible studies involving 1,194 participants were enrolled in the analysis. The NMA results revealed that compared with NB-UVB, carboxytherapy (OR = 32.35, 95 % CI: 1.79 to 586.05), Er: YAG laser+ topical 5% 5-FU (OR = 10.74, 95 % CI: 4.05 to 28.49), needling/micro-needling (OR = 3.42, 95 % CI: 1.18 to 9.88), betamethasone intra-muscular injection (OR = 3.08, 95 % CI: 1.17 to 8.13), topical tacrolimus (OR = 2.54, 95 % CI: 1.30 to 4.94), and oral Chinese herbal medicine compound (OR = 2.51, 95 % CI: 1.40 to 4.50) integrated with NB-UVB were more effective in excellent to complete re-pigmentation response rate (75 % or higher). In addition, NB-UVB+ Er: YAG laser+ topical 5 % 5-FU (OR = 0.17, 95 % CI: 0.04 to 0.67) and NB-UVB+ needling/micro-needling (OR = 0.24, 95 % CI: 0.06 to 0.88) were less likely evaluated as ineffective re-pigmentation response (25 % or less). The authors concluded that all combination therapies ranked higher than NB-UVB monotherapy in inducing successful re-pigmentation and avoiding failed treatment in patients with vitiligo. Comprehensive consideration, NB-UVB+ Er: YAG laser+ topical 5 % 5-FU and NB-UVB+ needling/micro-needling would be the preferred therapeutic approaches.

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## Policy History

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Effective: 06/20/2000

Next Review: 04/25/2024

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02-10000-13

Original Effective Date: 07/15/02

Reviewed: 04/25/24

Revised: 05/15/24

## Subject: Excimer Laser Therapy for Treatment of Dermatologic Conditions

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<a href="#">Position Statement</a>	<a href="#">Billing/Coding</a>	<a href="#">Reimbursement</a>	<a href="#">Program Exceptions</a>	<a href="#">Definitions</a>	<a href="#">Related Guidelines</a>
<a href="#">Other</a>	<a href="#">References</a>	<a href="#">Updates</a>			

### DESCRIPTION:

Excimer lasers (also called exciplex lasers) are proposed for the treatment of a variety of dermatological conditions including psoriasis, vitiligo, and atopic dermatitis. The laser utilizes xenon chloride to emit a wavelength of 308 nanometers (nm) and targets specific lesions or affected areas, thus limiting exposure to the surrounding normal tissues. The laser allows higher dosages which could result in fewer treatments to produce clearing. The original indication of the excimer laser was for patients with mild-to-moderate psoriasis, defined as involvement of less than 10% of the skin. Newer excimer laser devices are faster and more powerful than the original models, which may allow treatment of patients with more extensive skin involvement (10%-20% body surface area).

**Summary and Analysis of Evidence:** The Joint American Academy of Dermatology- National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with phototherapy (Elmets, et al., 2019) recommends for maximal efficacy, treatment with targeted UVB phototherapy for adults with localized plaque psoriasis should be carried out 2 to 3 times per week rather than once every 1 to 2 weeks. The recommendations also include excimer laser is more efficacious than an excimer light for the treatment of localized plaque psoriasis in adults. Excimer laser therapy is an established treatment for psoriasis. The evidence for treatment of vitiligo with excimer laser includes systematic reviews of randomized controlled trials, individual trials and retrospective studies. There is published literature to support the use of excimer laser therapy to treat psoriasis and vitiligo for individuals that have failed to respond to consecutive treatment.

## POSITION STATEMENT:

Use of an FDA-approved xenon chloride excimer laser (308 nm) **meets the definition of medical necessity** for the treatment of mild to moderate localized plaque psoriasis (comprising <20% body area) for members who have failed to respond to a consecutive 2 month trial of conservative treatment (i.e. topical agents, non-laser ultraviolet therapy).

Use of an FDA-approved excimer laser (308 nm) **meets the definition of medical necessity** for the treatment of moderate-to-severe localized plaque psoriasis.

**NOTE:** If the member fails to respond to an initial course of laser therapy for the treatment of localized plaque psoriasis additional therapy **does not meet the definition of medical necessity**.

Use of an FDA-approved excimer laser (308 nm) **meets the definition of medical necessity** for the treatment of vitiligo for members who have failed to respond to a consecutive 2 month trial of conservative treatment (i.e. topical agents, non-laser ultraviolet therapy).

**NOTE:** If the member fails to respond to an initial course of laser therapy for the treatment of vitiligo additional therapy **does not meet the definition of medical necessity**.

Use of excimer laser (308 nm) is considered **experimental or investigational** for all other indications including, but not limited to, the first line treatment of mild psoriasis, the treatment of generalized psoriasis, and the treatment of psoriatic arthritis. There is insufficient clinical evidence to permit conclusions on health outcomes.

## BILLING/CODING INFORMATION:

### CPT Coding:

96920	Excimer laser treatment for psoriasis; total area less than 250 sq cm
96921	Excimer laser treatment for psoriasis; 250 sq cm to 500 sq cm
96922	Excimer laser treatment for psoriasis; over 500 sq cm

### ICD-10 Diagnosis Codes That Support Medical Necessity:

L40.0 – L40.4 L40.8, L40.9	Psoriasis
L80	Vitiligo

## REIMBURSEMENT INFORMATION:

Total numbers of sessions per target area are limited to 30 in a 6-month period for codes 96920 – 96922 in any combination.

**Services in excess of this limitation are subject to review of the following documentation to support medical necessity:** attending physician initial assessment, attending physician history & physical, and attending physician visit notes that include documentation of failed response after 2 consecutive months of conservative therapy, member's response to laser therapy treatment including: reduction in Psoriasis Area and Severity Index (PASI) score or other objective response measurement; significant follicular pigmentation, and documentation that treatment is affecting the underlying condition.

## LOINC Codes:

DOCUMENTATION TABLE	LOINC CODES	LOINC TIME FRAME MODIFIER CODE	LOINC TIME FRAME MODIFIER CODES NARRATIVE
Physician Initial assessment	18736-9	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.
Physician history and physical	28626-0	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.
Attending physician visit note	18733-6	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.
Clinical notes and chart sections (i.e., documentation that shows failed response after 2 consecutive months of conservative therapy; patient's response to laser therapy treatment)	18741-9	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.

## PROGRAM EXCEPTIONS:

**Federal Employee Program (FEP):** Follow FEP guidelines.

**State Account Organization (SAO):** Follow SAO guidelines.

**Medicare Advantage products:** The following National Coverage Determinations (NCDs) were reviewed on the last guideline reviewed date: Laser Procedures (140.5) and Treatment of Psoriasis (250.1) located at [cms.gov](https://www.cms.gov).

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at [Coverage Protocol Exemption Request](#).

## DEFINITIONS:

No guideline specific definitions apply.

## RELATED GUIDELINES:

[Psoralens Plus Ultraviolet A \(PUVA\) Therapy \(Photochemotherapy\), 02-10000-16](#)

## OTHER:

None applicable.

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## COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 04/25/24.

## GUIDELINE UPDATE INFORMATION:

07/15/02	New Medical Coverage Guideline.
01/01/03	Annual HCPCS coding update.
07/15/03	Annual review. Added program exception for Medicare & More. Updated references.
07/15/04	Unscheduled review and revision; consisting of updated references and added investigational statement for excimer laser in the treatment of vitiligo.
05/15/05	Scheduled review and revision of guideline; consisting of updated references.
06/15/06	Scheduled annual review; eligible for coverage of psoriasis.
06/15/07	Annual review, maintained coverage and limitation language; reformatted guideline; references updated.
05/15/10	Guideline returned to active status; description section, position statements, reimbursement information section and references updated.

10/15/10	Revision; related ICD-10 codes added.
03/15/11	Annual review; position statements maintained and references updated.
07/01/11	Revision; formatting changes.
05/11/14	Revision: Program Exceptions section updated.
10/01/15	Revision; ICD10 coding section updated.
11/01/15	Revision: ICD-9 Codes deleted.
04/15/19	Review; Position statements, description, and references updated.
04/15/21	Review; Policy title, description, position statements, and references updated.
05/15/23	Review: Position statements maintained; references updated.
05/23/23	Update to Program Exceptions section.
01/01/24	Annual CPT/HCPCS coding update. Codes 96920-96922 revised.
05/15/24	Review: Position statements maintained; description and references updated.



## Medical Coverage Policy

Effective Date.....11/12/2023

Next Review Date.....6/15/2024

Coverage Policy Number ..... 0505

# Phototherapy, Photochemotherapy, Excimer Laser, Dermabrasion and Chemical Peels for Dermatologic Conditions

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## INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers



*must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.*

## Overview

This Coverage Policy addresses office-based phototherapy, photochemotherapy, excimer laser therapy, dermabrasion, and chemical peel for dermatologic conditions in the adult and pediatric populations. Phototherapy includes exposure to type A ultraviolet (UVA) radiation or type B ultraviolet (UVB) radiation. Photochemotherapy is exposure to UVA radiation following administration of a psoralen (e.g., methoxsalen, trioxsalen) (PUVA). Excimer laser therapy releases a spectrum of UVB wavelengths and is used to treat small, focused areas of the body. Home phototherapy may be indicated for a select subset of dermatologic conditions.

Dermabrasion and chemical peels are skin resurfacing procedures that remove the epidermis and superficial layers of skin to allow re-epithelialization. Dermabrasion and /or chemical peels are types of treatment that are generally employed for treating large areas where lesions are multiple and diffuse.

## Coverage Policy

**Coverage for home phototherapy devices varies across plans. Please refer to the customer's benefit plan document for coverage details.**

**Coverage for dermabrasion and/or chemical peel treatment varies across plans and may be subject to the provisions of a cosmetic and/or reconstructive surgery benefit, and may be governed by state mandates. Refer to the customer's benefit plan document for coverage details.**

### **Office-Based Phototherapy and Photochemotherapy**

**Office-based phototherapy and photochemotherapy\* are considered medically necessary when there is failure, intolerance or contraindication to conventional medical management (e.g., topical therapy, systemic immunomodulators, systemic immunosuppressants) for ANY of the following dermatologic conditions:**

- atopic dermatitis (i.e., atopic eczema)
- localized scleroderma
- cutaneous T-cell lymphoma (CTCL) (e.g., mycosis fungoides)
- lichen planus
- photodermatoses (e.g., polymorphic light eruption, actinic prurigo, chronic actinic dermatitis)
- psoriasis

### **Vitiligo**

**An initial regimen (i.e., for up to 12 weeks) of office-based phototherapy or photochemotherapy\* is considered medically necessary for the treatment of localized or generalized vitiligo when EITHER of the following criteria is met:**

- **vitiligo body surface area (BSA) involvement  $\leq 10\%$  with BOTH of the following:**
  - failure, intolerance or contraindication to a twelve consecutive week trial of at least ONE topical corticosteroid
  - failure, intolerance or contraindication to a twelve consecutive week trial of at least ONE topical calcineurin inhibitor (e.g., tacrolimus 0.03% or 0.1% ointment, pimecrolimus 1% cream)
- **vitiligo BSA involvement  $> 10\%$**

**Continued office-based phototherapy or photochemotherapy beyond the initial 12 weeks and for up to 52 weeks is considered medically necessary for the treatment of localized or generalized vitiligo when there is a beneficial clinical response to the previous course of treatment.**

**Continued office-based phototherapy or photochemotherapy beyond 52 weeks for up to and including 200 total treatments is considered medically necessary when there is a continued beneficial clinical response.**

**More than 200 treatment sessions of office-based phototherapy or photochemotherapy for vitiligo is considered not medically necessary.**

**\*Office-based phototherapy includes type A ultraviolet (UVA) radiation and type B ultraviolet (UVB) radiation. Photochemotherapy includes psoralens (P) and type A ultraviolet (UVA) radiation, known as PUVA photochemotherapy.**

#### **Other Conditions**

**Phototherapy or photochemotherapy is considered experimental, investigational, or unproven in any setting for any other indication, including EACH of the following dermatologic conditions:**

- alopecia areata
- cicatricial alopecias
- cutaneous herpes virus
- chronic ordinary urticaria
- chronic palmoplantar pustulosis
- chronic vesicular dyshidrotic eczema
- diabetic foot ulcer
- dyshidrotic eczema
- erythropoietic porphyria
- granuloma annulare
- herpesviridae
- onychomycosis
- palmoplantar eczema, acute
- psoriatic nail disease
- pityriasis rosea
- prurigo nodularis
- uremic pruritis
- urticaria pigmentosa (cutaneous mastocytosis)

#### **Office-Based Excimer Laser Therapy**

**Office-based targeted excimer laser therapy (i.e., 308 nanometers [nm]) is considered medically necessary for the treatment of localized, plaque psoriasis refractory to conservative treatment with topical agents and/or phototherapy.**

### **Vitiligo**

**An initial regimen (i.e., for up to 12 weeks) of office-based targeted excimer laser therapy (i.e., 308 nanometers [nm]) is considered medically necessary for the treatment of localized vitiligo when BOTH of the following criteria are met:**

- failure, intolerance or contraindication to a twelve consecutive week trial of at least ONE topical corticosteroid
- failure, intolerance or contraindication to a twelve consecutive week trial of at least ONE topical calcineurin inhibitor (e.g., tacrolimus 0.03% or 0.1% ointment, pimecrolimus 1% cream)

**Continued office-based targeted excimer laser therapy (i.e., 308 nanometers [nm]) beyond the initial 12 weeks and for up to 52 weeks is considered medically necessary for the treatment of localized vitiligo when there is a beneficial clinical response to treatment.**

**Continued office-based targeted excimer laser therapy (i.e., 308 nanometers [nm]) beyond 52 weeks up to and including 200 total treatments is considered medically necessary when there is a continued beneficial clinical response.**

**More than 200 treatment sessions of office-based targeted excimer laser therapy (i.e., 308 nanometers [nm]) for the treatment of vitiligo is considered not medically necessary.**

### **Other Conditions**

**Targeted excimer laser therapy (i.e., 308 nanometers [nm]) is considered experimental, investigational or unproven in any setting for any other indication, including EACH of the following dermatologic conditions:**

- alopecia areata
- atopic dermatitis (i.e., atopic eczema)
- cicatricial alopecias
- cutaneous herpes virus
- chronic ordinary urticaria
- chronic palmoplantar pustulosis
- diabetic foot ulcer
- dyshidrotic eczema
- erythropoietic porphyria
- granuloma annulare
- lichen planus
- onychomycosis
- palmoplantar eczema, acute
- pityriasis rosea
- prurigo nodularis
- psoriatic nail disease
- urticaria pigmentosa (cutaneous mastocytosis)

### **Home Phototherapy Devices**

**If coverage for home phototherapy devices is available, the following conditions of coverage apply:**

**An appropriately sized (e.g. hand wand for hand, two-foot panel for lower leg\*\*) ultraviolet B (UVB) home phototherapy device is considered medically necessary when the above criteria for office-based phototherapy and photochemotherapy are met with ALL of the following:**

- outpatient UVB phototherapy has been utilized, demonstrated to be beneficial and is expected to be long-term
- a prescription is needed for the device, and the device and treatment regimen are prescribed by a physician
- individual is motivated and compliant to prescribed usage

**\*\*Ultraviolet cabinets are generally not covered**

**Ultraviolet A (UVA) phototherapy in the home setting is considered not medically necessary.**

**The use of a tanning bed/unit for any reason in any setting is not considered medical in nature and as such does not meet the standard plan definition of Durable Medical Equipment. In addition, many benefit plans do not cover the use of a tanning bed/unit in any setting, including the home, for the treatment of dermatologic conditions because it is considered not medically necessary.**

### **Dermabrasion**

**If coverage for dermabrasion is available, the following conditions of coverage apply:**

**Dermabrasion (CPT 15780, 15781, 15782) is considered medically necessary for the treatment of actinic keratoses when BOTH of the following criteria are met:**

- lesions are diffuse (e.g.,  $\geq 10$  lesions) making targeted therapy impractical
- failure, contraindication or intolerance to one or more conventional field therapy treatments (e.g., topical 5-fluorouracil [5-FU, Efudex], topical diclofenac, photodynamic therapy [PDT], topical imiquimod [Aldara])

**Each of the following is considered cosmetic and not covered or reimbursable:**

- dermabrasion of ANY type (CPT 15780, 15781, 15782) for ANY other indication not listed above
- microdermabrasion or superficial dermabrasion (CPT 15783) for ANY indication

### **Chemical Peels**

**If coverage for chemical peel treatment is available, the following conditions of coverage apply:**

**Dermal chemical peels (CPT 15789, 15793) are considered medically necessary for the treatment of actinic keratoses when BOTH of the following criteria are met:**

- lesions are diffuse (e.g.,  $\geq 10$  lesions) making targeted therapy impractical
- failure, contraindication or intolerance to one or more conventional field therapy treatments (e.g., topical 5-fluorouracil [5-FU, Efudex], topical diclofenac, photodynamic therapy [PDT], topical imiquimod [Aldara])

**Each of the following is considered cosmetic and not covered or reimbursable:**

- dermal chemical peels (CPT 15789, 15793) for ANY other indication not listed above
- epidermal chemical peels (CPT 15788, 15792) for ANY indication

### **Chemical Exfoliation**

**Chemical exfoliation (CPT 17360) for treatment of acne vulgaris or ANY other indication is considered cosmetic and not medically necessary.**

## **General Background**

Dermatologic conditions are a common human illness. For example, according to the American Academy of Dermatology Association (ADD) (2021), atopic dermatitis affects up to 25% of children and 2-3% of adults and one in ten people will develop atopic dermatitis during their lifetime. Psoriasis affects approximately 7.5 million people in the United States. The ADD further states that in 2013 costs associated with treatment and lost productivity for those seeking treatment for atopic dermatitis was \$442 million. Total cost for treatment of psoriasis was estimated to be between \$51.7 and \$63.2 billion. Diagnosis of dermatologic conditions is made with a detailed history of the skin condition and a skin examination. Occasionally, additional diagnostic tools are necessary to make a definitive diagnosis (e.g., laboratory tests, skin biopsy, Wood's lamp, dermatoscope). The skin examination is focused on assessing the morphology and distribution of the lesions, color, consistency, and number and arrangement of the lesions. Treatment options vary greatly depending on the diagnosis and severity of symptoms and can include: antihistamines, medicated creams and ointments, laser therapy, ultraviolet radiation, and targeted prescription medications.

According to the National Eczema Association (2022), 19.3% of African American children have atopic dermatitis (eczema) compared to 16.1% of white and 7.8% of Asian children. It is important to note that many skin conditions (e.g., erythema, eczema, urticarial wheals, purpura, dry skin) may appear different between various skin pigmentation levels. For example, atopic dermatitis may appear brown, purple, or grey in individuals with brown or black skin and pink or red in individuals with lighter or white skin.

### **Office-Based Phototherapy and Photochemotherapy**

Phototherapy (e.g., actinotherapy) is defined as exposure to non-ionizing, ultraviolet (UV) radiation for therapeutic benefit by inducing DNA damage. The therapy involves exposure to type A ultraviolet (UVA) radiation or type B ultraviolet (UVB) radiation or various combinations of UVA and UVB. The differences in these ultraviolet light forms are the length of the waves. UVA wavelength is 320-400 nanometers [nm], broadband (bb) UVB is 280-320 nm and narrowband (nb) UVB is 311-312 nm. UVA is further broken down into UVA1 (340-400 nm) and UVA2 (320-340 nm). The longer wavelengths emit a lower energy level. UVA bulbs, for example, are used in tanning beds for cosmetic effects because they promote tanning using lower energy with less erythema than UVB. Photochemotherapy is exposure to UVA radiation following administration of a psoralen (e.g., methoxsalen, trioxsalen) given orally, topically, or in a bath which makes the skin more susceptible to the effects of UVA (PUVA). Combination therapy includes phototherapy or photochemotherapy with topical agents, such as tar, anthralin and corticosteroids, or with systemic agents, such as retinoids and methotrexate. Phototherapy and chemotherapy are proposed for numerous indications (e.g., atopic dermatitis, localized scleroderma, psoriasis, dyshidrotic eczema, chronic ordinary urticaria). The duration and number of treatments depends on the dermatologic condition; type, number, and location of the lesions; skin type; type of therapy (e.g., UVA, UVB, PUVA); dosage; and the response to treatment. Treatment is typically administered two to three times per week until the condition clears.

Evidence in the published peer-reviewed scientific literature, including systematic reviews, randomized controlled trials and case series, as well as professional societies and organizations support the safety and effectiveness of phototherapy and photochemotherapy for the treatment of atopic dermatitis, localized scleroderma, cutaneous T-cell lymphoma, lichen planus, photodermatoses, psoriasis, and vitiligo for patients who do not tolerate or are unresponsive to conventional medical management (e.g., oral immunosuppressive agents, biologic agents, topical and oral steroids) (Valipour, et al., 2020; Buense, et al., 2012; Khandpur and Sharma, 2012; Paul, et al., 2012; Farnaghi, et al., 2011; Dayal, et al., 2010; Jain, et al., 2010; Mahajan, et al., 2010; Sivanesan, et al., 2009; Kroft, et al., 2008; Ponte, et al., 2010; Tzaneva, et al., 2010; Pavlotsky, et al., 2008; Trott, et al., 2008; Brockow, et al., 2007; Erkin, et al., 2007; Kirke, et al., 2007; Meduri, et al., 2007; Schiener, et al., 2007; Sezer, et al., 2007; Wackernagle, et al., 2007; Boztepe, et al., 2006; Brown and Reynolds, 2006; Gambichler, et al., 2006; Gokdemir, et al., 2006; Goldinger, et al., 2006; Kreuter, et al., 2006; Wise, 2006; Vongthongsri, et al., 2006; Yones, et al., 2006; Asawanonda, et al., 2005; Berneburg, et al., 2005; El-Mofty, et al., 2005; Kollner, et al., 2005; Lebwohl, et al., 2005; El-Mofty, et al., 2004; Ibbotson, et al., 2004; Tahir, et al., 2004; Saricaoglu, et al., 2003; Scheinfeld, et al., 2003; Whitaker, et al., 2003).

**U.S. Food and Drug Administration (FDA):** Phototherapy and photochemotherapy light sources are approved by the FDA 510(k) process as Class II phototherapy units for a variety of skin disorders. Examples of phototherapy light sources include: 3 Series NeoLux (Daavlin Distributing Co., Bryan, OH), 7 Series Phototherapy Device (Daavlin Distributing Co., Bryan, OH), the Houva Phototherapy System with PhotoSense II™ (National Biological Corporation, Inc., Beachwood, OH), and the Psoria-Shield AURORA (Psoria-Shield, Utica, NY).

**Atopic Dermatitis:** Atopic dermatitis, or atopic eczema, is a chronic skin condition characterized by a dry, itchy rash on the face, elbows, hands, knees, and/or feet. In addition to skin care and avoidance of substances that might irritate the skin, topical therapy, and oral corticosteroid are standard treatment options. For severe cases in adults, immunosuppressants may be prescribed.

**Literature Review:** The evidence in the published peer-reviewed scientific literature in the form of systematic reviews and randomized controlled trials supports UVB, nbUVB, and UVA phototherapy, PUVA, and combination treatments as safe, effective, and well-tolerated therapies for atopic dermatitis. Studies reported appreciative improvement in symptoms and in some cases long-term remission (Musters, et al., 2021; Garritsen, et al., 2014; Tzaneva, et al., 2010; Brown and Reynolds, 2006; Wise, 2006; Meduri, et al., 2007).

**Professional Societies/Organizations:** The American Academy of Dermatology (AAD) (2014) recommended phototherapy for the treatment of atopic dermatitis following failure of first-line therapy, including emollients, topical steroids, and topical calcineurin inhibitors. Phototherapy can also be used for treatment in chronic disease as a maintenance therapy. The light modality, dosing and scheduling is based on various factors, such as phototherapy technique, skin type, skin cancer history, and use of photosensitizing medication. Although AAD stated that home phototherapy may be considered for a subset of patients who are unable to go to an office setting, they noted that there are no studies that document the safety and efficacy of home phototherapy for AD.

**Localized Scleroderma:** Localized scleroderma, also known as morphea, is a rare autoimmune and auto-limiting disease of unknown etiology characterized by sclerosis of the connective tissue and microcirculatory changes leading to thickening of the skin from excess collagen production. Resolution usually takes place within months to years however, 10% of people will develop atrophic, deforming lesions. Clinical presentation includes "erythematous or violaceous macules, with smooth surface and white-yellowish center, which progressively becomes depressed and hardened." This is referred to as the inflammatory stage. The stage of stable disease is apparent



as the macules progress into a “white-ivory color on the central atrophic area, surrounded by a sclerotic plaque”. Treatment (e.g., medicated creams and ointments, UV light therapy, steroids, immunosuppression) is not always needed and depends on the severity of disease. (Buense, et al., 2012).

**Literature Review:** Systematic reviews, randomized controlled trials, and case series support the efficacy of UVA and PUVA for the treatment of localized scleroderma (Albuquerque, et al., 2019; Buense, et al., 2012; Kroft, et al., 2008; Kreuter, et al., 2006; El-Mofty, et al., 2004)

**Cutaneous T-cell Lymphoma (CTCL):** Cutaneous T-cell lymphoma (CTCL) is a slowly evolving form of non-Hodgkin lymphoma of the T-cell. Early stages of the disease may present as distinctive lymphoid dermatoses, such as parapsoriasis, poikiloderma atrophicum vasculare, follicular mucinosis (alopecia mucinosa), and pityriasis lichenoides. Two-thirds of CTCL cases are mycosis fungoides (MF), a form of CTCL that evolves from scaly skin patches and plaques. Sezary syndrome is an aggressive form of mycosis fungoides. CTCL may initially be treated with topical chemotherapy agents. PUVA is a widely used treatment for early cutaneous T-cell lymphoma, mycosis fungoides and Sezary syndrome. UVB for MF and Sezary is typically administered 2–3 times a week with  $\geq 24$  hours between treatments. A response may be seen within one month of initiation of treatment. PUVA is also typically given 2–3 times a week with 48 hours between treatments. Long-term maintenance is proposed after the initial clearing. Frequency of treatments will depend on the extent of the disease and recurrence rate (Vieyra-Garcia, et al., 2018; Olsen, et al., 2016; Zandi, et al., 2010; National Cancer Institute, 2016; Olsen, et al., 2007; Gokdemir, et al., 2006; El-Mofty, et al., 2005).

**Literature Review:** Randomized controlled trials and case series support the safety and efficacy of phototherapy and photochemotherapy for the treatment of CTCL. The results from the clinical trials reported significant improvement to complete remission of T-cell lymphoma and mycosis fungoides (Farnaghi, et al., 2011; Ponte, et al., 2010; Gokdemir, et al., 2006; El-Mofty, et al., 2005; Scheinfeld, et al., 2003; Whitaker, et al., 2003). A Cochrane systematic review (Valipour, et al., 2020) did not find evidence to challenge the role of PUVA as a first-line treatment of MF based upon the results of five studies.

**Professional Societies/Organizations:** The National Cancer Institute (2023) lists PUVA and UVB phototherapy as treatment options for mycosis fungoides and Sezary syndrome with early cutaneous stages achieving the best responses. Treatment options depend on the stage of the disease.

In their guidelines for the treatment of primary cutaneous lymphomas, the National Comprehensive Cancer Network® (NCCN®) (2023) lists phototherapy as treatment options for mycosis fungoides and Sezary syndrome recommending UVB and nbUVB for limited or localized skin involvement and UVB, nbUB, PUVA, or UVA1 for the treatment of generalized skin involvement. Treatment varies based on the disease stage.

In a consensus statement on the management of mycosis fungoides and sezary syndrome, the United States Cutaneous Lymphoma Consortium stated that UVB or PUVA may be considered for individuals with stage IA, IB, or IIA mycosis fungoides. They added that PUVA may be more effective for thick plaques or folliculotropic involvement than UVB because UVA has better skin penetration properties (Olsen, et al., 2016).

**Lichen Planus:** Lichen planus is an inflammatory disease that usually affects the skin and/or the mouth and is characterized by recurrent, itchy, inflammatory rash and/or lesions. Since there is no cure for lichen planus, treatment is aimed at relieving symptoms. Milder cases may be treated

with corticosteroid creams and ointments, anti-inflammatory drugs, and antihistamines. More severe cases may require oral or injectable corticosteroids, phototherapy and photochemotherapy.

**Literature Review:** Although the evidence supporting the efficacy of phototherapy and photochemotherapy for lichen planus is primarily in the form of case series and retrospective reviews, these modalities are established treatment options for this condition when conventional therapies are not effective, not tolerated or are contraindicated. Partial and complete response have been reported in patients following therapy (Iraji, et al., 2011; Pavlotsky, et al., 2008; Wackernagel, et al., 2007; Saricaoglu, et al., 2003; Reichrath, et al., 2002).

**Photodermatoses (e.g., Polymorphic Light Eruption, Actinic Prurigo, Chronic Actinic Dermatitis):** Photodermatoses refers to skin conditions that are aggravated by sunlight. The primary photodermatoses include polymorphic light eruption, actinic prurigo, and chronic actinic dermatitis, also known as photosensitivity dermatitis. Solar urticaria is a rare photodermatoses characterized by pruritis, erythema, pain and wheal formation. Treatment options include avoiding sun exposure, using sunscreens, and topical and/or oral steroids. Phototherapy is viewed as a mainstay of treatment for severe cases.

**Literature Review:** A limited number of studies in the form of randomized controlled trials and case series have reported that photodermatoses can be successfully treated with UVA, UVB, UVA/UVB, nbUVB phototherapy, and PUVA. Phototherapy and photochemotherapy are recognized treatment options for these conditions (Gambichler, et al., 2006; Ibbotson, et al., 2004).

**Psoriasis:** Psoriasis is a skin disease involving thickened, red areas covered with silvery scales and characterized by chronic, recurrent exacerbations and remissions. The forms of psoriasis include plaque, pustular (e.g., palmoplantar), inverse, erythrodermic and guttate. Medical management of psoriasis may include bath solutions, moisturizers, topical corticosteroid ointments and creams, vitamin D ointment, retinoid gel and coal tar (i.e., Goeckerman treatment). Phototherapy and photochemotherapy are established treatment options for patients with psoriasis who do not respond to medical treatment.

**Literature Review:** Systematic reviews, randomized controlled trials, and case series support the safety and efficacy of phototherapy and photochemotherapy for the treatment of psoriasis. Studies have reported favorable response to treatment using bbUVB, nbUVB, PUVA, and followed by phototherapy (e.g., balneophototherapy). Phototherapy is considered an essential treatment option for psoriasis (Chen, et al., 2013; Paul, et al., 2012; Khandpur and Sharma, 2012; Dayal, et al., 2010; Jain, et al., 2010; Mahajan, et al., 2010; Sivanesan, et al., 2009; Trott, et al., 2008; Brockow, et al., 2007; Erkin, et al., 2007; Kirke, et al., 2007; Schiener, et al., 2007; Sezer, et al., 2007; Boztepe, et al., 2006; Goldinger, et al., 2006; Yones, et al., 2006; Vongthongsri, et al., 2006; Asawanonda, et al., 2005; Kollner, et al., 2005; Lebwohl, et al., 2005; Berneburg, et al., 2005; Tahir, et al., 2004).

**Professional Societies/Organizations:** The American Academy of Dermatology and the National Psoriasis Foundation issued a joint guideline on the management of psoriasis in pediatric patients that recommends the use of narrowband UVB is recommended as a treatment option for moderate to severe plaque and guttate psoriasis in the pediatric population. PUVA may be beneficial but has limited supporting evidence (Menter, et al., 2020).

In their guidelines on the treatment of psoriasis, the American Academy of Dermatology (AAD) (Menter, et al., 2010) stated that UVB phototherapy is safe and effective and nbUVB phototherapy is generally preferable and has improved efficacy compared to bbUVB phototherapy. UVB phototherapy can be given in the office or at home. PUVA is also effective and may result in long remissions, but may increase the risk for squamous cell carcinoma and malignant melanoma. The

duration of treatment using phototherapy or photochemotherapy varies depending on the type of psoriasis, skin type, ultraviolet dosing, and whether nbUVB (e.g., 15–20 treatments), bbUVB (e.g., 20–25 treatments), or topical or systemic PUVA is used. Improvement may be seen within 2–4 weeks and 8–40 treatments.

In an evidence-based clinical consensus document, the National Psoriasis Foundation Medical Board stated that systemic therapy and/or phototherapy (broad and narrowband phototherapy, photochemotherapy (PUVA), systemic agents, and biologics) are recommended for patients with psoriasis affecting greater than 5% BSA; for those with less than 5% BSA affected in vulnerable areas, such as the face, genitals, hands or feet; and for other forms of psoriasis, including but not limited to erythrodermic, pustular and guttate. In addition, patients with limited affected areas and inadequate response to localized therapy or impairment in physical or mental functioning should also be considered candidates for systemic and/or phototherapy treatment (Pariser, et al., 2007).

In 2019 the American Academy of Dermatology and the National Psoriasis Foundation released a joint guideline re-affirming that ultraviolet phototherapy serves as a safe and effective treatment option of psoriasis for those with failing first line topical treatment or patients wishing to avoid systemic medication (Elmets, et al., 2019).

**Vitiligo:** Vitiligo is a disease resulting in a loss of pigment cells (i.e., melanocytes), producing white patches. The contrast between the white patches and unaffected skin can result in disfigurement leading to stigmatization, isolation, and low self-esteem. This contrast is most prominent in those with darker skin tones. The etiology of vitiligo is widely accepted as unknown; however, could possibly be identified as an autoimmune disease. Self-management of vitiligo includes avoiding sun exposure and using sunscreens and self-tanning dyes. In some cases, the use of interventions that repigment the skin is only temporary and may not result in long-term or permanent results. Treatment of vitiligo using phototherapy has developed into a standard of care by proving its efficacy and safety.

**Literature Review:** Phototherapy and photochemotherapy is supported by the scientific literature as a safe and effective treatment option for vitiligo and is an established treatment option for patients who are unresponsive to conservative therapy. Follow-up data on the long-term effectiveness of phototherapy maintaining pigmentation are limited, but relapse has been reported in up to 25–44% of patients within 12–18 months following cessation of nbUVB therapy. Some patients have reportedly relapsed within three months (Lopes, et al., 2016, Whitton, et al., 2015; Nicolaidou, et al., 2009).

#### **Office-Based Excimer Laser Therapy**

Excimer laser, also called exciplex laser, is a form of ultraviolet laser proposed for the treatment of various dermatologic conditions including, atopic dermatitis, psoriasis and vitiligo. An excimer laser releases a spectrum of 308-nm UVB wavelengths and is used to treat small, focused areas of the body (e.g., 2 X 2 centimeters). Laser therapy is proposed to increase the precision and delivery of UVB energy to targeted tissue. The increased precision results in a faster therapeutic effect and decreases the total number of treatments needed, limits the amount of UV radiation exposure, and decreases the risk of skin cancer (Feldman, 2019). The hand-held lasers are good for hard to treat areas such as elbows, knees, palms, soles of feet and scalp. This precision makes total-body treatment with laser therapy difficult. Some propose that laser therapy is effective, safe and well tolerated when limited to less than 20% of the body surface. Treatments are typically given two to three times a week on nonconsecutive days, last for 15-30 minutes, and are given for 4–36 weeks resulting in improvement of the condition. The number of treatments required depends on multiple factors including the condition being treated, the severity of the condition, skin type, and response to treatment. A minimum of 48 hours between treatments is advised.

Excimer laser therapy is an established treatment option for localized, plaque psoriasis (Menter, et al., 2010; Nicolaidou, et al., 2009). Although the therapy has been proposed for other conditions, the evidence does not support its use nor is it an established standard treatment for other conditions. Phototherapy, photochemotherapy, and excimer laser therapy are contraindicated in individuals with known photosensitivity, porphyria, or systemic lupus erythematosus.

**U.S. Food and Drug Administration (FDA):** Excimer lasers are approved by the FDA 510(k) process. Not all excimer lasers are approved for the treatment of the same dermatological conditions. Excimer lasers include but are not limited to the following:

- XTRAC XL Excimer Laser System (PhotoMedex, Inc. Carlsbad, CA) is approved for the treatment of psoriasis, vitiligo, leukoderma, and atopic dermatitis (FDA, 2004b).
- 308 Dermatological Excimer Lamp Phototherapy System (Quantel Medical, Hasbrouck Heights, NJ), distributed by National Biological Corporation, is approved for the treatment of psoriasis and vitiligo (FDA, 2007).
- Excilite™ and Excilite-μ (Cynosure, Inc., Chelmsford, MA) monochromatic excimer light systems are approved for the treatment of “leukoderma, psoriasis, vitiligo, eczema, and seborrheic dermatitis, for skin types I to VI” (FDA, 2005).
- Levia Phototherapy System (Lerner Medical Devices, Inc., Los Angeles, CA) is “intended for use in UVB phototherapy in all skin types for the treatment of psoriasis including scalp psoriasis, vitiligo, atopic dermatitis (eczema) seborrheic dermatitis and leucoderma”. The Levia has a fiber-optic brush used for areas of the skin covered with hair (FDA, 2004).
- XTRAC Momentum Excimer Laser System (Strata Skin Sciences, Inc., St. Petersburg, FL) is indicated for the treatment of psoriasis, vitiligo, atopic dermatitis, and leukoderma (FDA, 2020).

**Psoriasis:** Excimer laser therapy is supported by the scientific literature and is an established treatment option for patients with psoriasis that is unresponsive to topical agents or phototherapy (Mudigonda, et al., 2012; Nisticò, et al., 2009; He, et al., 2007; Lapidoth, et al., 2007; Amornpinyokeit and Asawanonda, 2006; Goldinger, et al., 2006; Nisticò, et al., 2006; Kollner, et al., 2005; Taibjee, et al., 2005; Taneja, et al., 2003; Trehan and Taylor, 2002; Rodewald, et al., 2002; Feldman, et al., 2002).

**Professional Societies/Organizations:** In 2019, the American Academy of Dermatology and the National Psoriasis Foundation released a joint guideline recommending targeted UVB phototherapy, including excimer, for use in adults with localized plaque psoriasis. Treatment should occur 2-3 times per week (Elmets, et al., 2019).

In a guideline on the treatment of psoriasis, the American Academy of Dermatology (AAD) recommends the use of excimer laser therapy for the treatment of mild, moderate or severe psoriasis with less than 10% body surface area involvement. Initial dosage depends on the skin type and plaque characteristics and thickness. Treatment is typically administered two to three times a week until the condition clears (average of 10–12 weeks). Mean remission time is reported to be 3.5–6 months (Menter, et al., 2010).

In an evidence-based clinical consensus document, the National Psoriasis Foundation Medical Board recommended excimer laser treatments for localized therapy for psoriasis that affects less than 5% body surface area (Pariser, et al., 2007).

**Vitiligo:** Evidence in the published peer-reviewed scientific literature is in the form of open, prospective studies and systematic reviews that support the safety and effectiveness of excimer laser therapy for the treatment of medically refractory vitiligo. The data suggests that there are no significant differences in outcomes between excimer lamps and excimer lasers. Pruritis, burning

sensation, and dryness were noted as mild side effects that did not interrupt treatment. (Lopes, et al., 2016; Whitton, et al., 2015; Nisticò, et al., 2009).

### **Phototherapy, Photochemotherapy, and Excimer Laser Therapy for Other Conditions:**

Phototherapy, photochemotherapy and/or excimer laser therapy have been proposed for numerous other dermatologic conditions including atopic dermatitis, cicatricial alopecias, chronic ordinary urticaria, chronic palmoplantar pustulosis, chronic vesicular dyshidrotic eczema, diabetic foot ulcers, dyshidrotic eczema or acute palmoplantar eczema (vesicular eczema, pompholyx, cheiropompholyx or pedopompholyx), erythropoietic porphyria, granuloma annulare, herpesviridae or cutaneous herpes virus (e.g., herpes simplex type 1 and 2, varicella-zoster virus, human herpesvirus 7, Kaposi sarcoma), lichen planus, onychomycosis, pityriasis rosea, psoriatic nail disease, prurigo nodularis or nodular prurigo, uremic pruritis and/or urticaria pigmentosa (cutaneous mastocytosis).

There is insufficient evidence in the published peer-reviewed literature to support phototherapy, photochemotherapy and excimer laser therapy for these other conditions, nor are these therapies an established treatment option. Studies are primarily in the form of retrospective reviews, case series with small patient populations and short-term follow-ups (e.g., five weeks to eight months) or case reports. Outcomes were conflicting and/or reported no improvement. Some studies combined phototherapy with topical steroids and have not investigated phototherapy as a monotherapy for a specific condition (Gupta, et al., 2021; Obeid, et al., 2020; Contreras-Ruiz, et al., 2019; Ma, et al., 2019; Qureshi, et al., 2019; Simonsen, et al., 2017; Wang, et al., 2017; Fertig and Tosti, 2016; Su, et al., 2016; Crowley et al., 2015; Manhart and Rich, 2015; Sanchez-Regana, et al., 2015; Armstrong, et al., 2014; Bristow, 2014; Dillenburg, et al., 2014; Gupta and Simpson, 2013; Ledon, et al., 2012; Kelley and Rashid, 2011; Ko, et al., 2011; Navarini, 2011; Alkhalifah, et al., 2010; Brenninkmeijer, et al., 2010; Tan, et al., 2010; Lim, et al., 2009; Nisticò, et al. 2009; Engin, et al., 2008; Sezer, et al., 2007; Baltás, et al., 2006; Gambichler, et al., 2005; Petering, et al., 2004; Trehan and Taylor, 2004).

**Alopecia Areata:** Alopecia areata is an autoimmune disorder affecting hair follicles and sometimes the nails. The hair stops growing and suddenly starts falling out in patches from the roots. The patches of hair loss enlarge and then grow back. The patient can experience total scalp hair loss (alopecia totalis), loss of all hair on the body (alopecia universalis) or diffuse thinning of the hair (alopecia areata incognita). Pitting and drainage of the nails may be seen in 10% of cases. Alopecia sometimes starts after a stressful event. There is no reliable cure for the disease. Spontaneous remission occurs in up to 80% of patients. Scalp creams, corticosteroids (topical and injectable) and contact immunotherapy have been used but have not been shown to alter the course of the disease. (New Zealand Dermatologic Society, 2015, updated 2022; British Association of Dermatology, 2012)

**Literature Review:** Phototherapy, PUVA and excimer laser therapy have been proposed as treatment options but there is insufficient evidence in the published peer-reviewed scientific evidence to support these therapies for the treatment of alopecia areata. There is little documented evidence that UVB is effective and the limited success and long-term safety, side effects and a high relapse rate have curtailed the use of PUVA. Overall, studies investigating the effectiveness of UVB, PUVA, and excimer laser are primarily in the form of case series, retrospective reviews, and a randomized controlled trial with small patient populations (n=3–18), short-term follow-ups (e.g., five weeks to six months), and heterogeneous treatment parameters. Outcomes varied depending on the type of alopecia and some patients had no response to therapy (Kianfar, et al., 2022; Gupta, et al., 2021; Alkhalifah, et al., 2010).

A meta-analysis completed by Gupta et. al. (2021) concluded that there were only four studies (n=105) testing the efficacy of 308-nm excimer laser therapy for alopecia areata. The study

compared the excimer laser treatment versus a non-treatment group. The author concluded that treatment was effective vs the non-treatment group ( $p < 0.0009$ ). While this study does conclude that excimer laser therapy can be effective for alopecia areata, it is limited by the small patient populations, heterogeneity of outcome measures and the need for larger controlled studies.

### **Atopic Dermatitis (i.e., Atopic Eczema)**

**Literature Review:** There are a limited number of studies evaluating excimer laser therapy for the treatment of atopic dermatitis. Studies are primarily in the form of case series or retrospective reviews with small patient populations and short-term follow-ups (Brenninkmeijer, et al., 2010; Baltás, et al., 2006).

Brenninkmeijer et al. (2010) conducted a within patient, randomized controlled trial ( $n=10$ ) to compare the safety and efficacy of 0.05% topical clobetasol propionate (CP) ointment to excimer laser (EL) therapy for the treatment of prurigo atopic dermatitis. The patients had more than four symmetrical prurigo nodules on the lower and upper extremities that had persisted for six months or longer. Treatment was randomized to either the right or left side of the patient's body. Laser therapy was administered for ten weeks. Compared to baseline scores, both sides showed a significant improvement of mean Physician Assessment of Individual Signs (PAIS) ( $p < 0.001$ ) during follow up weeks 14–34. At week 34, the EL treated nodules had a significantly better PAIS score compared to the CP treated nodules ( $p < 0.05$ ). More patients reported marked improvement following EL ( $n=7$ ) compared to CP ( $n=4$ ). Less relapse of disease was seen following EL treatment. There was no significant difference in the pruritus scores between the two treatment groups. Author noted limitations of the study included the small patient population, selection of more severely affected patients, loss of blinding due to sustained hyperpigmentation in the EL group, and the use of various radiant exposures.

**Professional Societies/Organizations:** Due to the lack of evidence, the American Academy of Dermatology (AAD) (2014) does not recommend laser therapy as a treatment modality for atopic dermatitis.

**Cicatricial Alopecia:** Cicatricial (scarring) alopecia (hair loss), also called scarring alopecia or scarring hair loss, refers to a diverse group of rare disorders that destroy the hair follicles, replaces them with scar tissue, and causes permanent hair loss. Cicatricial alopecias are classified as primary or secondary. Primary cicatricial alopecias are inflammatory disorders of the scalp in which the hair follicle is the target of destruction. Primary disorders are classified as lymphocytic or neutrophilic. Lymphocytic cicatricial alopecias include lichen planopilaris, frontal fibrosing alopecia (FA), central centrifugal cicatricial alopecia (CCCA) and discoid lupus erythematosus. Neutrophilic cicatricial alopecias include folliculitis decalvans and dissecting cellulitis. Secondary cicatricial alopecia is destruction of the hair follicle from disorders that cause diffuse scarring of the dermis, including burns, radiation, severe skin infections, localized scleroderma, and scalp tumors. Symptoms of itching, burning, pain, or tenderness usually signal ongoing activity. Signs of scalp inflammation include redness, scaling, and pustules. In some cases there are very few signs and symptoms. A punch biopsy of the scalp is indicated to identify the type of inflammation, degree of activity and other changes in the scalp. Treatment depends on the type of cicatricial alopecia and includes anti-inflammatory agents (e.g., topical or intralesional steroids), calcineurin inhibitors, tetracyclines, hydroxychloroquine, and cyclosporin. Discontinuation of traumatic hair care practices is an essential aspect of treatment of CCCA. Hair restoration surgery or scalp reduction are surgical treatment performed for cosmetic benefits and are only considered in individuals with a one to two year period of inactive disease (National Organization for Rare Disorders. [NORD], 2018; Shapiro, 2018; NORD, 2016; New Zealand Dermatology Society, 2014).



**Literature Review:** Studies have primarily been in the form of retrospective reviews and case series with small patient populations and short-term follow-ups. Additional high quality studies are needed to assess the safety and efficacy of phototherapy, photochemotherapy, and excimer laser therapy for the treatment of cicatricial alopecia (Fertig and Tosti, 2016; Navarini, 2011).

**Chronic Vesicular Dyshidrotic Eczema:** Chronic vesicular dyshidrotic eczema is a condition more commonly seen in young adults and those who have: another type of eczema, hay fever, an allergy (e.g., nickel or cobalt), sweaty hands, a family history of eczema, a personal history as a metal worker or mechanic, or have worked with cement. It is characterized by tiny, itchy, fluid filled blisters either on the hands, feet, or both. Treatment consists of soaks and cool compresses, corticosteroids, antihistamines, moisturizers or a barrier cream, pimecrolimus or tacrolimus ointment, or ultraviolet light therapy (American Academy of Dermatology Association, 2020).

**Literature Review:** Evidence in the peer reviewed literature is limited to comparative and non-controlled trials with short-term follow-up and small patient populations. Additional high quality randomized controlled trials are necessary to evaluate the long-term safety and efficacy of phototherapy, photochemotherapy, or excimer laser therapy for the treatment of vesicular dyshidrotic eczema (Sezer, et al., 2007; Petering, et al., 2004).

Petering et al. (2004) randomized high-dose UVA1 to PUVA for the treatment of chronic vesicular dyshidrotic eczema on the palms and backs of hands of 27 patients. Each hand was randomly treated with a different therapy. At the end of three weeks, the Dyshidrosis Area and Severity Index (DASI) scores improved to nearly half the pretreatment scores in both hands with no significant differences between the treatments.

**Diabetic Foot Ulcer:** Diabetic foot ulcers, characterized by full thickness wounds below the level of the ankle, are the result of peripheral insensitivity, neuropathy, and tissue damage. A lack of sensation leads to a reduction in awareness of potentially damaging foreign bodies and injuries on the part of the individual. It is that between 15–25% of individuals with diabetes will develop diabetic foot ulcers at some point in their lives. Disparities exist with prevalence ranging from 2% in high income countries to 15–25% in low and middle income countries. The presence of diabetic foot ulcers carries risk for infection, hospitalization, and amputation.

**Literature Review:** A Cochrane systematic review (Wang, et al., 2017) of randomized controlled trials evaluated phototherapy for the treatment of open foot ulcers in adult diabetics. Included studies compared 1) phototherapy with sham phototherapy, no phototherapy, or other physical therapy modalities; 2) different forms of phototherapy; or 3) phototherapy of different output power, wavelength, power density, or dose range. Eight studies (n=316) met inclusion criteria. No studies reported valid data for time to complete wound healing. Meta-analysis of four studies (n=116) indicated that more wounds treated with phototherapy experienced more healing compared with no phototherapy or placebo. Results from individual trials (n=16–84) generally suggested that after two to four weeks of treatment phototherapy may have resulted in a greater reduction in ulcer size. Analyses for quality of life (n=28) and amputations (n=23) showed no clear differences between phototherapy and no phototherapy or placebo. No significant adverse events were reported. The level of evidence was considered low due to the small patient populations, methodological flaws and unclear or high risk of bias. Large, well-designed randomized controlled trials are needed to confirm whether phototherapy is an effective treatment option for diabetic foot ulcers.

**Generalized (Disseminated) Granuloma Annulare:** Generalized granuloma annulare (GA) presents with numerous benign pruritic erythematous or skin-colored papules and plaques affecting, most often, the trunk and extremities that will spontaneously resolve over the course of a few years. The lesions range in size from a few millimeters to a few centimeters in diameter. In

individuals with darker skin color, the lesions may present with hypo or hyperpigmentation. The exact cause of GA is unknown, and it can affect both children and adults. Skin biopsy is often required to confirm a diagnosis of generalized GA due to the variable characteristics of the lesions and potential overlap with other skin conditions. The decision to treat generalized GA is based upon the appearance of the lesions and the intractable pruritis associated with the condition. Although a standard of care for treatment does not exist, the preferred initial therapy to treat generalized GA is systemic therapy with hydroxychloroquine since widespread application of topical therapy can be challenging with numerous lesions. Other options include oral isotretinoin and dapsone. PUVA, UVB, nbUVB, UVA, and excimer laser have also been proposed for the treatment of generalized GA (Brodell, 2023; Brodell, 2021; Mukovozov, et. al., 2021).

**Literature Review:** The evidence published in the peer-reviewed literature for the treatment of generalized GA with phototherapy and photochemotherapy consists of case reports and small case series limited by small patient populations, short-term follow-up, and heterogeneity of study designs and treatment parameters. (Mukovozov, et al., 2022; Muylaert, et al., 2017; Cunningham, et al., 2016; Pavlovsky, et al., 2016; Yong, et al., 2016).

Mukovozov, et al. (2021) conducted a systematic review of thirty-one case series to evaluate the safety and efficacy of light and laser-based treatments for the treatment of localized and generalized GA. There were 336 participants (67.6% had generalized GA) in total ranging in age from 6–89 years of age with 74.6% being female. Cohort, cross-sectional, and case-controlled studies, and case series were considered for inclusion in the review if they evaluated the use of phototherapy (of any type) in individuals of any age diagnosed with GA (localized, generalized, or unspecified). The interventions evaluated in the review included: PUVA, photodynamic therapy, UVB/nbUVB/excimer laser, UVA, and lasers. Outcomes evaluated included complete resolution, partial resolution, and no response. However, these outcomes were not defined. The duration of follow-up was not specified. A synthesis of quantitative evidence was not possible due to heterogeneity of study design and patient characteristics. Overall, the studies were found to have a moderate risk of bias. PUVA was evaluated in 119 participants with generalized GA and found that 57%, 26%, and 17% achieved complete resolution, partial resolution, and no response, respectively. UVA1 was evaluated in 47 participants with generalized GA and found that 45%, 23%, and 32% achieved complete resolution, partial resolution, and no response, respectively. UVB/nbUVB was evaluated in 37 participants with generalized GA and found that 35%, 22%, and 43% achieved complete resolution, partial resolution, and no response, respectively. The mean time to achieve either complete or partial response was 2.1 and 2.2 months respectively for PUVA, 0.8 and 0.8 respectively for UVA1, and 3.1 and 2.4 months respectively for UVB/nbUVB/excimer. Mean time to response data was not categorized by GA subtype. Higher response rates were observed for localized GA compared to generalized GA. Author noted limitations of the review included: heterogeneity in study designs, patient populations, treatment interventions, and outcome measures preventing generalizability of the results; lack of high-level evidence, and small sample sizes. High quality studies with longer follow-up, larger samples sizes, focused patient populations and treatment parameters are needed to support the use of phototherapy and photochemotherapy in individuals with generalized GA.

**Lichen Planus:** Lichen planus is an inflammatory disease that usually affects the skin and/or the mouth and is characterized by recurrent, itchy, inflammatory rash and/or lesions. Since there is no cure for lichen planus, treatment is aimed at relieving symptoms. Milder cases may be treated with corticosteroid creams and ointments, anti-inflammatory drugs, and antihistamines. More severe cases may require oral or injectable corticosteroids, phototherapy and photochemotherapy.

**Literature Review:** There is insufficient evidence in the published peer-reviewed literature to support the efficacy of excimer laser therapy for the treatment of lichen planus. Studies are

primarily in the form of case studies with small patient populations (Trehan and Taylor, 2004; Dillenburg, et al., 2014).

In a randomized controlled trial, Dillenburg, et al. (2014) compared the application of topical clobetasol propionate gel (0.05%) three times a day (n=21) to laser irradiation (InGaAlP; MM Optics, São Carlos, São Paulo, Brazil)) three times a week (n=21) for the treatment of atrophic and erosive oral lichen planus. Both groups showed initial improvement. At the 60-day follow-up the laser group had one recurrence and the clobetasol group had 10 recurrences. At the 90-day follow-up the laser group showed a significant improvement in the resolution of lesions ( $p<0.001$ ) and exhibited more hyperkeratotic lesions and fewer atrophic/erosive lesions than the clobetasol group ( $p<0.001$ ). The difference in recurrence between the groups at day 90 was not significant ( $p=0.276$ ). There were no reported side effects in the laser group. According to the authors, this is the first known comparison study of laser therapy vs. clobetasol. Additional studies with larger patient populations and long-term follow-up are needed to validate the results of this study.

**Herpesviridae:** Herpesviridae, also known as herpesviruses, is a common viral infection of the skin including but not limited to: herpes simplex viruses (i.e., HSV-1 and HSV-2), varicella zoster virus, Epstein-Barr virus, human cytomegalovirus, human herpes 6, human herpes 7, and Kaposi's sarcoma virus. Common among herpesviruses is a vesicle on an erythematous base along with a period of latency. Transmission most commonly occurs either through close physical contact or contact with infected secretions. The gold standard for treatment is the use of antivirals such as acyclovir (Whitley, 1996).

Kelley and Rashid (2011) conducted a systematic review to evaluate published studies investigating phototherapy for the treatment of Herpesviridae (n=267). Eleven clinical trials and case reports included patients with herpes simplex, varicella-zoster, human herpesvirus, and Kaposi sarcoma. Studies included case reports or case series and randomized controlled trials with small patient populations, short-term follow-ups and various types of herpes. Long-term studies with large patient populations comparing phototherapy with conventional treatment modalities are needed. Phototherapy regimens for Herpesviridae have not been established.

**Onychomycosis:** Onychomycosis is an infection in the nail bed and nail plate caused by any type of fungus (e.g., yeasts, nondermatophyte molds). The three main types of dermatophytic onychomycosis (also called tinea unguium) are distal subungual, proximal subungual, and white superficial. Dermatophyte fungi (e.g., *Trichophyton* sp.) are more likely to be pathogenic than nondermatophyte fungi, also referred to as molds (e.g., *Fusarium* sp.). Other types of onychomycosis include endonyx and totally dystrophic. One of several fingernails and/or toenails may be involved, but onychomycosis is more common on toenails. Onychomycosis can cause nail discoloration, thickening, irritation, pain and detachment of the nail plate. The presence of diabetes or other immunocompromised conditions may increase the risk of cellulites or other types of bacterial infection.

Treatment depends on the underlying cause and the patient's comorbidities. Oral medications (e.g., terbinafin and itraconazole) may be used in immunocompromised patients. A topical antifungal nail lacquer with or without an oral agent may be indicated. Surgery may be used to treat an isolated nail infection involving only one digit or for the treatment of a dermatophytoma (i.e., collection of dermatophytes in solid form under the nail). *Candida* onychomycosis responds to oral agents, but it is prone to relapse if the underlying reason for the infection is not resolved. Long-term recurrence rates of 20%–50% have been reported.

Because of the varied response and side effects of oral agents and the high relapse rates, additional non-systemic treatment modalities are being investigated. Phototherapy and laser therapy have been proposed for the treatment of onychomycosis but there is insufficient evidence

in published clinical trials to support the safety and efficacy of these modalities (Durme, 2012; Gupta, et al., 2012; Hoy, et al., 2012).

**Literature Review:** Ma et al. (2019) conducted a systematic review and meta-analysis on available literature to evaluate the safety and effectiveness of laser treatments for onychomycosis. Thirty-five studies met the inclusion criteria of randomized controlled trial or clinical study in which the onychomycosis group received only laser treatment; onychomycosis diagnosed by mycological exam; study purpose related to the efficacy of laser treatment for onychomycosis; patients had not been treated with systemic antifungal drugs during the preceding six months and had no other clinical manifestations associated with skin diseases; and mycological cure rate and clinical cure rate of diseased nail reported. Studies were excluded if case report; duplicate publication; conference papers, systematic reviews, and meta-analyses; and studies in which laser treated group received other forms of treatment. The thirty five studies included five randomized controlled trials (n=1723 patients; n=4278 diseased nails). Adverse reactions were reported to be transient hemorrhage and mild to moderate burning sensations. There were no serious adverse reactions reported. The primary outcome measure recorded was mycological cure rate and safety profile. The overall mycological cure rate was 63.0% (95%CI 0.53-0.73); the mycological cure rate associated with the 1064-nm Nd: YAG laser was 63.0% (95%CI 0.51-0.74); and that of CO2 lasers was 74.0% (95%CI 0.37-0.98). While the author concluded that laser treatment of onychomycosis is safe and effective, of the thirty five studies only five are RCTs. Those RCTs are noted to have small patient populations; heterogeneity of protocol and treatment lasers; and short term follow-ups.

Bristow (2014) conducted a systematic review of the literature to evaluate the effectiveness of laser therapy for the treatment of onychomycosis. Two randomized controlled trials, four comparative studies with no control groups and four case series met inclusion criteria. Although some studies reported improvement in onychomycosis, the outcomes were conflicting and the study methodology was heterogeneous and of poor quality. Some studies reported recurrence suggesting that laser therapy only had a temporary effect. Additional limitations of the studies included small patient populations (n=8–131) with predominantly short-term follow-ups of < 24 weeks. Several of the studies excluded patients with severe or dystrophic disease. The authors noted that there is no consensus on laser effectiveness.

Gupta and Simpson, 2013 conducted a systematic review to determine the efficacy of laser therapy for the treatment of onychomycosis. A review of the literature identified three basic science articles, five peer-reviewed articles, and four pending clinical trials. The authors concluded that studies with large patient populations, mycologic examination before and after treatment, long-term follow-ups and standardized outcome measures are needed to determine if laser therapy is effective for the treatment of onychomycosis or comparable to traditional pharmacotherapeutics.

**Psoriatic Nail Disease:** Psoriatic nail disease, psoriatic nail dystrophy or nail psoriasis occurs in up to 55% of individuals with skin psoriasis, but nail psoriasis can occur without the presence of skin psoriasis. Nail psoriasis may involve pitting, discoloration (white or yellow-red), onycholysis (separation of the nail plate from the nail bed), scaling under the nail (subungual hyperkeratosis), crumbling, thickening and horizontal lines in the nail. Psoriasis can affect fingernails and toenails. Nail psoriasis can lead to pain, tenderness, functional disability and secondary bacterial or fungal infections. Scrapings and/or biopsy may be necessary to confirm the diagnosis.

Topical therapies such as corticosteroids, calcipotriol, tazarotene, and tacrolimus creams and ointments may be helpful in mild or early nail psoriasis. For individuals who also have severe skin psoriasis and/or psoriatic arthritis, a systemic or biologic treatment can reduce symptoms overall. Nail improvement may lag behind clearing of psoriasis plaques on the body by several months. It

can take six months to a year for an affected nail to grow out and be replaced by a new nail (New Zealand Dermatology Society, 2021; Manhart and Rich, 2015; Crowley, et al., 2015; Schons et al., 2014).

**Literature Review:** There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of phototherapy, photochemotherapy, or excimer laser therapy for the treatment of psoriatic nail disease. Studies are primarily in the form of small retrospective reviews with short term follow-up (Crowley et al., 2015; Manhart and Rich, 2015; Sanchez-Regana, et al., 2015; Armstrong, et al., 2014).

**Professional Societies/Organizations:** Based on a systematic review, a 2015 consensus statement for the treatment of nail psoriasis from the Medical Board of the National Psoriasis Foundation does not recommend phototherapy, PUVA or excimer laser therapy for the treatment of nail psoriasis (Crowley, et al., 2015).

**Uremic Pruritis:** Also known as chronic kidney disease-associated pruritus, uremic pruritis is frequently seen with end-stage renal disease. The cause is uncertain however, parthormone, histamine, calcium, and magnesium are suspected to be causative factors. Treatment options consist of topical treatment with or without anti-inflammatory compounds, systemic treatment with gabapentin or other drugs, phototherapy, or acupuncture (Mettang and Kremer, 2015).

Simonsen et al. (2017) conducted a systematic review of the literature to assess treatment options for uremic pruritus. A total of 44 randomized controlled trials evaluating 39 different treatments were included in the review. Regarding phototherapy, four studies (n=112) met inclusion criteria. Three studies compared UV-B to UV-A therapy and one study evaluated narrow-band UVB. Dosages varied based on the patient's skin characteristics. The two studies using broadband UV-B indicated a significant benefit in favor of UV-B therapy over UV-A. However, the study comparing narrow-band UV-B to UV-A showed no statistically significant benefit of narrow-band UV-B therapy compared to UV-A therapy. Sunburn and tanning were noted side effects of the UV-B therapy. Additional studies are needed to support the effectiveness of phototherapy for the treatment of uremic pruritus.

Ko et al. (2011) conducted a randomized controlled trial to evaluate the efficacy of nbUVB (n=11) compared to a control group (n=10) who received no treatment for uremic pruritis in patients with stage III–V chronic kidney disease. At the 12-week follow-up, both groups showed significant improvement in the visual analogue scores (VAS) but there were no significant differences between the groups. Based on an interview questionnaire, the nbUVB groups reported improvement in the percentage of affected skin (p=0.004), in difficulty falling to sleep (p=0.02) and sleep disturbance (p=0.01). Phototherapy did not have a significant effect in reducing pruritis intensity compared to the control group.

### **Home Phototherapy**

In some cases, UVB phototherapy may be transitioned to home use under the supervision of a physician if the individual has extensive, widespread disease (e.g., psoriasis) that is going to require long-term use and office-based phototherapy has been proven to be effective. Home devices emitting predominantly narrowband UVB phototherapy are used primarily for the treatment of psoriasis and require that the patient be motivated, reliable, adherent to instructions, able to administer the treatment correctly, keep records of exposure, and attend regular follow-up visits. Opponents to home therapy cite issues related to poor patient compliance, suboptimal efficacy, and greater potential for phototoxicity, erythema, burns, carcinogenesis and photoaging. Some propose limiting home phototherapy to those with overwhelming difficulties in traveling to a facility. Home devices are available in a variety of sizes to accommodate whole body treatment, hand/foot treatment, or localized treatment. Once the size of unit is determined, a decision will be

made by the physician as to the type of UVB light source indicated for treatment. The physician may prescribe bbUVB or nbUVB. The number of bulbs needed will be determined based on the size of the unit. (Lapolla, et al., 2011; Menter, et al., 2010; Rajpara, et al., 2010).

UVA phototherapy is primarily used in combination with psoralen (i.e., PUVA) for the treatment of disease (e.g., psoriasis) and is administered in an outpatient setting. On its own, UVA is ineffective in treating conditions such as psoriasis and atopic dermatitis and is therefore not generally used in the home setting.

Tanning beds, or units, which typically emit UVA, are used for self-tanning solely for the purpose of improvement in appearance (i.e., cosmetic); they are not medical devices designed to be used to administer physician-prescribed treatment for a dermatologic condition.

**U.S. Food and Drug Administration (FDA):** The Panosol II® line of devices (National Biological Corporation, Inc., Twinsburg, OH) first received FDA approval through the 510(k) process December 24<sup>th</sup>, 1990 and are indicated for numerous dermatological conditions. This series of devices is available in either two or six foot stand-alone panels and is capable of providing narrowband UVB and/or UVA therapy.

Hand and foot UVB units may be in the form of a combined unit or may be individual units. A combined unit has the appearance of a desk and allows the patient to place their hands and feet into the unit, receiving treatment simultaneously. One such example is the Hand/Foot II™ device (National Biological Corporation, Inc., Twinsburg, OH) that originally received FDA approval through the 510(k) process on July 24, 1987. This device is designed for localized treatment of the hands or feet and is capable of providing narrowband UVB, broadband UVB, or UVA therapy. On March 20<sup>th</sup>, 2017, the FDA issued a class two recall for this device noting that the device may be able to be turned on with the key switch rather than the timer. As such, individual patients were contacted and replacement devices were distributed. Defective devices were returned. Individual hand and foot units may have the appearance of a tabletop device such as the SolRX™ 500 Series (Solarc Systems, Inc., Ontario, Canada) which originally received FDA approval through the 510(k) process on September 10, 2003. The device used the National Biological Hand/Foot device as its predicate and is indicated, with a prescription, as spot treatment of psoriasis, vitiligo, and atopic dermatitis.

Handheld devices are available as well including the DermaPal with Digital Timer device (Daavlin Distributing Co., Bryan, OH) that received FDA approval through the 510(k) process on January 18, 2008. This device is intended for use under the direction of a physician with a prescription for the treatment of psoriasis, vitiligo, and atopic dermatitis. The Levia Phototherapy System (Lerner Medical Devices, Inc., Grand Rapids, MI) received FDA approval through the 510(k) process on February 13<sup>th</sup>, 2004. This device is indicated to provide UVB therapy for the treatment of scalp psoriasis, vitiligo, atopic dermatitis, seborrheic dermatitis, and leukoderma. Another example of a handheld device is the Skylit Phototherapy System (Skylit Medical, La Jolla, CA) that was given FDA approval through the 510(k) process on May 23, 2017. This device is indicated for the treatment of psoriasis, vitiligo, atopic dermatitis, seborrheic dermatitis, and leukoderma. It differs from the other examples given in that it works with an app that serves as the main interface to operate the device. A prescription is submitted by the ordering provider with all treatment parameters entered into the app. The user can then set treatment times while the app delivers the correct dosage and time limit for treatment. This device also integrates the assistance of a "careprovider" who's function it is to educate, encourage compliance, monitor for non-responsiveness, and communicate with the prescribing physician. The device is also known under the trade names "Clarify" and "Zerigo".



**Literature Review:** A Hayes Technology Brief (2013; reviewed 2015) stated that although the overall body of evidence is low, the data suggested that home UVB for the treatment of moderate to severe psoriasis is effective and well tolerated. Patient adherence was generally high and there were no identified safety issues. The Brief included one multicenter randomized controlled study, one 2-phase prospective comparative study, and three prospective case series.

In a single-blind randomized controlled trial, Koek et al. 2009 compared the outcomes of outpatient UVB therapy (n=98) to home UVB therapy (n=98) for patients treated for mild to severe psoriasis. After the completion of therapy, the first 105 consecutive patients were followed for one year. Outcomes were measured by the self-administered psoriasis area and severity index (SAPASI) and the psoriasis area and severity index (PASI). Treatment effect indicated by the mean decline in the PASI and SAPASI scores was significant ( $p < 0.001$ ) and similar across groups ( $p > 0.3$ ) indicating that home therapy was as good as and, in some cases, superior (SAPASI 90) to outpatient therapy. Improvement in quality life for home patients was rated as a 42% compared to 23% for outpatients. Total cumulative doses of ultraviolet B light and the occurrence of short-term side effects were not significantly different between the groups.

### **Dermabrasion and Chemical Peels**

Dermabrasion and/or chemical peels are established dermatological treatments for specific skin conditions and may be recommended for the treatment of precancerous skin lesions (i.e., actinic keratoses); however, in many cases these methods of treatment do not improve function and are employed for the improvement of personal appearance. Treatments intended to improve personal appearance or that do not improve functional deficits are considered cosmetic in nature.

Precursor squamous cell carcinoma (SCC) lesions include those that are precancerous (i.e., actinic keratoses [AK]) and lesions that are squamous cell carcinoma in situ (e.g., Bowen's disease). According to National Comprehensive Cancer Network (NCCN) Guidelines™ Basal Cell Skin Cancers (NCCN, 2023) and Squamous Cell Skin Cancers (NCCN, 2023), both lesion types can lead to invasive squamous cell carcinoma and potential metastasis; therefore, early treatment is recommended. While there are a variety of techniques available with comparable effectiveness for precancer-type lesions, chemical peels and dermabrasion may be considered accepted treatments for actinic keratoses. Dermabrasion and chemical peels are not listed in the NCCN guidelines as accepted treatment for squamous cell carcinoma in situ (i.e., Bowen's disease). There are no precursor lesions for basal cell carcinoma.

**Dermabrasion:** Dermabrasion is a surgical procedure that resurfaces the texture of the skin by removing its top layer using a mechanical instrument (such as a high-speed rotary abrasive wheel) to remove the layers of skin. Dermabrasion is also referred to as abrasion, salabrasion, microdermabrasion, dermaplaning or sanding the skin. Laser abrasion (Tunable Dye, CO<sup>2</sup> and Ruby lasers) and chemabrasion (phenol, trichloroacetic acid and glycolic acid) are modalities of treatment that are used in place of conventional dermabrasion.

Dermabrasion, most often performed for the purpose of removing acne scars, tattoos or fine wrinkles, is performed in an office setting using a local anesthetic. Depending on the severity of the lesion and area being treated, a second treatment may be required for complete results. Following treatment, the individual can expect discoloration and scabbing to occur, which will last for five to seven days. Discoloration and swelling can last for two to three months while the area is healing. Scarring after the skin has healed is rare.

Dermabrasion has proven effective in treating multiple recalcitrant actinic keratoses (AK) lesions in cases where numerous AK lesions (e.g., more than 10) have been documented and where lesions are diffuse with severe actinic damage. AK lesions are precancerous skin lesions that occur on the epidermis (outer layer of skin) and result from long-term exposure to the sun. The

condition is also commonly referred to as solar keratosis, senile keratosis, senile hyperkeratosis, keratoma senile and keratosis senilis. Microscopically, AK lesions show varying degrees of atypia and abnormal maturation and may be further classified as atrophic, hyperkeratotic, bowenoid, acantholytic, lichenoid and pigmented (Gupta, 2012). AKs are the most commonly treated type of premalignant lesion and are considered precursor lesions to squamous cell carcinoma (SCC). In general, treatment of AK lesions is divided into lesion directed therapy or field therapy (Gupta, 2012). Lesion directed therapy targets a specific lesion. Field therapy is used to treat areas involving subclinical lesions and areas involving multiple clinical lesions making it impractical to treat each lesion separately. Topical field therapies that have proven effective for AK lesions include 5-fluorouracil, imiquimod, diclofenac, ingenol gel, photodynamic therapy, dermabrasion and chemical peels. Dermabrasion for other dermatological conditions is considered cosmetic.

Microdermabrasion is a non-invasive, non-surgical cosmetic procedure that can be performed either by a physician or in some cases, by individuals in a home setting. The noninvasive treatment exfoliates or removes the top layer of skin (i.e., stratum corneum) and is frequently performed to diminish the signs of aging. Dermabrasive procedures that resurface the superficial layer of skin, including but not limited to those used to reduce the signs of aging, are considered cosmetic.

**Chemical Peel:** A chemical peel, also referred to as chemexfoliation, involves the application of a chemical solution with the goal of producing controlled removal of layers of the epidermis and superficial dermis. Although used primarily on the face, chemical peels can be used on other areas such as the neck and hands. Chemical peel solutions damage the outer layers of the skin and stimulate collagen formation, resulting in dermal regeneration and improvement of the appearance of the skin. Categories of chemical peels include superficial, medium-depth and deep.

Superficial peels (epidermal peels) extend down to the stratum granulosum and papillary dermis. This type of chemical peel is recommended as an effective treatment for conditions which include, but are not limited to, mild photoaging, acne, and melasma. Alpha-hydroxy acids (AHAs), such as glycolic, lactic or fruit acid, are used in superficial peeling to rejuvenate and resurface sun-damaged skin, soften the appearance of pores, treat fine wrinkles and reduce uneven pigmentation. Superficial chemical peels that affect the superficial layer of skin are considered cosmetic.

Dermal chemical peels may be either medium-depth or deep. Medium-depth and deep chemical peels penetrate deeper into the dermis. Medium-depth peels are used to treat moderate photoaging, actinic keratoses, pigmentary dyschromias and mild acne scarring. Trichloroacetic acid (TCA) with Jessner's solution or 70% glycolic acid is used for medium-depth peeling to treat surface wrinkles and sun-damaged skin. Phenol 88%, one of the strongest peels, may also be used as a medium-depth peel.

Deep chemical peels are used to penetrate further into the dermis and are often used to treat more severe photodamage, actinic keratosis, acne scars and pigmentary dyschromias. Baker's solution and 50% or greater TCA are solutions typically used in deep chemical peeling to diminish coarse facial wrinkles and correct pigment abnormalities.

Similar to dermabrasion, medium and deep chemical peels are a type of field therapy employed for treating recalcitrant AK when there are numerous lesions (e.g., more than 10) and other types of field therapy have not been effective. When used to treat other epidermal or dermal conditions, such as photo-aging, scarring, wrinkles or uneven pigmentation, chemical peels in the absence of a functional deficit are considered cosmetic and not medically necessary.

When used for the treatment of acne vulgaris, the clinical effectiveness of chemical peel treatments has not been firmly established (Zaenglein, et al., 2016). Some studies have suggested that superficial or epidermal peels using AHAs may have a comedolytic effect on comedonal acne lesions by loosening follicular impaction and may be appropriate for individuals with widespread lesions for whom standard treatment has failed. However, the clinical effectiveness of superficial peels in the overall management of patients with active acne has not been established through well-designed trials. Additionally, medium and deep chemical peels are not considered appropriate for active acne as they have been shown to exacerbate the inflammation associated with acne. As noted in guidelines of care for the management of acne vulgaris, the American Academy of Dermatology acknowledges that large, multicenter, double-blinded control trials comparing chemical peels to placebo and comparing different types of chemical peels for the treatment of acne are lacking. Glycolic and salicylic acid peels may be used for the treatment of non-inflammatory acne (comedonal) although treatments require multiple applications and results are not long-lasting (Zaenglein, et al., 2016). According to the guidelines of care, chemical peels may result in mild improvement of comedonal acne, a recommendation based on inconsistent or limited quality patient-oriented evidence (B recommendation). Overall, the evidence available in the published, peer-reviewed scientific literature is insufficient and does not lend strong support to the clinical utility of any type of dermal chemical peel or chemical exfoliation in the treatment of acne vulgaris.

### **Cosmetic Indications**

When performed solely for the purpose of altering appearance or self-esteem, or to treat psychological symptomatology or psychosocial complaints related to one's appearance, dermabrasion and chemical peels are considered cosmetic and not medically necessary. Examples of conditions for which dermabrasion and chemical peels are considered cosmetic include but are not limited to the following:

- rhinophyma
- rosacea
- scar revision
- treatment of photo-aged skin
- treatment of uneven pigmentation
- treatment of rhytids (i.e., wrinkles)
- removal of tattoos

**U.S. Food and Drug Administration (FDA):** Some chemical peels may be prepared in an office setting and may involve the use of various chemical agents, including ingredients considered to be cosmetic. As a result, FDA approval or clearance may not be relevant.

Dermabrasion is considered a noninvasive surgical procedure and as such is not regulated by the FDA. However, devices, such as those used for microdermabrasion, are regulated by the FDA.

### **Professional Societies/Organizations:**

Several professional societies/organizations, including but not limited to the American Society of Plastic Surgeons and the American Osteopathic College of Dermatology, provide information regarding treatments aimed at improving the appearance of various dermatological conditions. For most dermatological conditions, specific recommendations such as a formal guideline or a position statement could not be found.

The American Academy of Dermatology (2016) published guidelines of care for the management of acne vulgaris. Per the report, inconsistent or limited-quality patient-oriented evidence is present for the use of chemical peels. Existing studies note the need for multiple treatments and short-term effects with only mild improvement in comedonal acne. They further acknowledge that large,

multicenter, double-blinded control trials comparing peels to placebo and comparing different peels are lacking (Zaenglein, et al., 2016).

Guidelines issued by the National Comprehensive Cancer Network (NCCN) for squamous cell skin cancer (SCC) were updated in 2023. The presence of actinic keratoses (AK) increases an individual's risk for developing SCC. The guideline recommends aggressive treatment of AK and squamous carcinoma in situ lesions at first development as part of the identification and management of high-risk patients. Treatments for precancerous lesions (i.e., actinic keratosis): chemical peels (trichloroacetic acid) and ablative skin resurfacing (laser, dermabrasion) have been proven effective for treatment. AK with an atypical clinical appearance, or that does not respond to appropriate therapy should be biopsied for histologic evaluation (NCCN, 2023).

Guidelines issued by the National Comprehensive Cancer Network (NCCN) for basal cell skin cancer treatment are dependent on risk stratification. Curettage and electrodesiccation (C&E) and surgical excision are the preferred treatments for low-risk basal cell skin cancers. Those with high-risk basal cell skin cancer are recommended to undergo surgical excision (e.g. Mohs surgery). If the patient is not a surgical candidate, radiation or systemic therapy is proposed (NCCN, 2023).

## Coding Information

### Notes:

1. This list of codes may not be all-inclusive.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

### Office-Based Phototherapy and Photochemotherapy

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

CPT®* Codes	Description
96900	Actinotherapy (ultraviolet light)
96910	Photochemotherapy; tar and ultraviolet B (Goeckerman treatment) or petrolatum and ultraviolet B
96912	Photochemotherapy; psoralens and ultraviolet A (PUVA)
96913	Photochemotherapy (Goeckerman and/or PUVA) for severe photoresponsive dermatoses requiring at least 4-8 hours of care under direct supervision of the physician (includes application of medication and dressings)

### Office-Based Excimer Laser Therapy

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

CPT®* Codes	Description
96920	Laser treatment for inflammatory skin disease (psoriasis); total area less than 250 sq cm
96921	Laser treatment for inflammatory skin disease (psoriasis); 250 sq cm to 500 sq cm
96922	Laser treatment for inflammatory skin disease (psoriasis); over 500 sq cm

### **Home Phototherapy Devices**

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

<b>HCPCS Codes</b>	<b>Description</b>
E0691	Ultraviolet light therapy system, includes bulbs/lamps, timer and eye protection; treatment area 2 square feet or less
E0692	Ultraviolet light therapy system panel, includes bulbs/lamps, timer and eye protection, 4 foot panel
E0693	Ultraviolet light therapy system panel, includes bulbs/lamps, timer and eye protection, 6 foot panel

**Considered Specifically Excluded Under Some Benefit Plans:**

<b>ICD-10-CM Diagnosis Codes</b>	<b>Description</b>
E0694	Ultraviolet multidirectional light therapy system in 6 foot cabinet, includes bulbs/lamps, timer and eye protection

### **Dermabrasion**

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

<b>CPT® Codes</b>	<b>Description</b>
15780	Dermabrasion; total face (eg, for acne scarring, fine wrinkling, rhytids, general keratosis)
15781	Dermabrasion; segmental, face
15782	Dermabrasion; regional, other than face

<b>ICD-10-CM Diagnosis Codes</b>	<b>Description</b>
L57.0	Actinic keratosis

**Not Covered or Reimbursable:**

<b>ICD-10-CM Diagnosis Codes</b>	<b>Description</b>
	All other codes

### **Superficial/Microdermabrasion**

**Not Covered or Reimbursable:**

<b>CPT®* Codes</b>	<b>Description</b>
15783	Dermabrasion; superficial, any site (eg, tattoo removal)

<b>ICD-10- CM Diagnosis Codes</b>	<b>Description</b>
	All codes

### **Chemical Peels**

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

<b>CPT®* Codes</b>	<b>Description</b>
15789	Chemical peel, facial; dermal
15793	Chemical peel, nonfacial; dermal

<b>ICD-10- CM Diagnosis Codes</b>	<b>Description</b>
L57.0	Actinic keratosis

### **Not Covered or Reimbursable:**

<b>ICD-10- CM Diagnosis Codes</b>	<b>Description</b>
	All other codes

### **Epidermal Chemical Peels**

### **Not Covered or Reimbursable:**

<b>CPT®* Codes</b>	<b>Description</b>
15788	Chemical peel, facial; epidermal
15792	Chemical peel, nonfacial; epidermal

<b>ICD-10- CM Diagnosis Codes</b>	<b>Description</b>
	All codes

### **Chemical Exfoliation**

**Considered Not Medically Necessary:**

<b>CPT®* Codes</b>	<b>Description</b>
17360	Chemical exfoliation for acne (eg, acne paste, acid)

<b>ICD-10-CM Diagnosis Codes</b>	<b>Description</b>
	All codes

**\*Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.**

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## Revision Details

Type of Revision	Summary of Changes	Date
Focused review	<ul style="list-style-type: none"> <li>Content from CP 0505 Dermabrasion and Chemical Peels moved into this CP.</li> <li>Title change.</li> <li>Revised policy statements for: dermabrasion for any other indication, microdermabrasion or superficial dermabrasion, dermal chemical peels, and epidermal chemical peels.</li> </ul>	11/12/2023

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# Clinical Policy: Laser Therapy for Skin Conditions

Reference Number: CP.MP.123

Date of Last Revision: 03/23

[Coding Implications](#)

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

## Description

Targeted phototherapy utilizes non-ionizing ultraviolet radiation with therapeutic benefit. Phototherapy is an efficacious local therapy that provides several advantages to traditional and biologic systemic therapies. Excimer lasers are monochromatic 308 nm xenon chloride lasers that are approved to treat certain inflammatory skin diseases. This policy describes the medical necessity requirements for excimer laser based targeted phototherapy.

## Policy/Criteria

- I. It is the policy of health plans affiliated with Centene Corporation® that excimer laser based targeted phototherapy is **medically necessary** for the following indications after the failure of topical treatments:
  - A. Localized plaque psoriasis with <10% body surface area (BSA) involvement, individual lesions, or more extensive disease;
  - B. Vitiligo;
  - C. Atopic dermatitis;
  - D. Cutaneous T-cell lymphoma (e.g., mycosis fungoides/ Sézary Syndrome).
- II. It is the policy of health plans affiliated with Centene Corporation that the evidence is insufficient to draw conclusions regarding the efficacy of excimer laser targeted phototherapy for the following indications:
  - A. Patients with photosensitivity disorders;
  - B. For the treatment of all other conditions than those specified above.

## Background

Targeted phototherapy uses a localized delivery of ultraviolet light to facilitate therapeutic relief of some conditions. Ultraviolet light is predominantly absorbed by skin DNA, leading to the generation of pyrimidine dimers, pyrimidine, and (6-4) photoproducts which are either repaired or marked for arrest or cell death through the cell's checkpoint machinery.<sup>5</sup> Various spectra of ultraviolet A (UVA) and ultraviolet B (UVB) wavelengths are utilized to treat a varying array of inflammatory skin disorders, including narrowband, broadband, and excimer lasers, as well as combinations of UVA and UVB with topical, systemic, biologic, and chemotherapeutic regimens.<sup>1</sup> Additionally, phototherapy is cost effective and avoids the immunosuppressive effects that often accompany traditional and biologic based systemic therapies.

Excimer lasers are monochromatic 308nm xenon chloride lasers that provide a safe and selective approach to treating dermatological conditions. Excimer lasers are associated with significant T-cell depletion, alterations in apoptosis-related molecules, reductions in proliferation indices, and immunomodulatory mechanisms.<sup>6</sup> An early study by Feldman *et al* assessed the efficacy of excimer lasers for the treatment of mild to moderate psoriasis in a multicenter study. The authors noted that 84% of the patients reached the primary outcome of at least 75% improvement of their



plaques within 1 month.<sup>7</sup> Another study by Rodewald *et al* compared the excimer laser to a non-intervention, placebo cohort, as well as other standard topical treatments for psoriasis.<sup>8</sup> The laser and topical calcipotriene had similar efficacies but both were more effective than topical tazarotene or fluocinonide and the time to achieve 75% improvement favored the excimer laser.<sup>8</sup> Therefore, laser was comparable to or more effective than other standard treatments for psoriasis.<sup>8</sup>

According to a joint updated guideline from the American Academy of Dermatology, National Psoriasis Foundation, the excimer laser is recommended for use in adults with localized plaque psoriasis (including palmoplantar psoriasis) <10% BSA, for individual lesions, or in patients with more extensive disease (recommendation based on consistent, good quality patient oriented evidence.) Excimer laser is also recommended in the treatment of scalp psoriasis in adults (based on inconsistent or limited-quality patient-oriented evidence.)<sup>13</sup>

The initial treatment dose of the excimer laser depends on the individual's skin type, plaque characteristics, and thickness, with subsequent doses adjusted in accordance to the patient's clinical response and side effects.<sup>1,13</sup> Treatment takes place two to three times per week until a patient is clear of symptoms. According to a separate guideline on children from the American Academy of Dermatology, National Psoriasis Foundation, excimer laser may be used in children with psoriasis and may be efficacious and well tolerated, but these options have limited supporting evidence.<sup>14</sup>

The European Dermatology Forum and the British Association of Dermatologists provide guidelines for the management of vitiligo.<sup>3,4</sup> The consensus of the European Dermatology Forum is that targeting phototherapy should be indicated for localized vitiligo and for small lesion of recent onset and childhood vitiligo.<sup>3</sup> Notably, Alhowaish *et al* documented the effectiveness of excimer laser treatments in vitiligo in 23 separate articles that included case studies, randomized controlled studies, retrospective analyses, randomized blinded studies, and controlled comparative studies.<sup>9</sup> Although the response time and the duration of response varied, the excimer laser therapy was generally effective across all of the studies.<sup>9</sup> While several treatment options are available for vitiligo, targeted laser therapy delivers high intensity light to the desired depigmented area to avoid exposure to surrounding neighboring healthy skin.<sup>17</sup>

Atopic dermatitis (eczema) is a chronic, pruritic, inflammatory skin disease with clinical presentation of dry skin, severe pruritus and cutaneous hyperreactivity to various environmental stimuli. Skin hydration with emollients and moisturizers is a key component of first-line therapy. Other topical treatments, i.e., anti-inflammatory therapy with topical corticosteroids or calcineurin inhibitors can be effective in controlling pruritus. When topical therapy alone is not enough, narrowband ultraviolet B (NBUVB) or ultraviolet A1 (UVA1) phototherapy can be added. Patients with moderate to severe disease despite topical therapy may require systemic treatment such as dupilumab. Narrowband ultraviolet B (NBUVB) phototherapy is also an alternative. However, phototherapy is not suitable for infants and young children. Phototherapy can be administered in the office two to three times weekly.

Mycosis fungoides (MF) and Sézary syndrome (SS) are common subtypes of cutaneous T cell lymphoma (CTCL). MF is a mature T cell non-Hodgkin lymphoma that presents in the skin but

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has potential involvement of the lymph nodes, blood, and viscera. Skin lesions include patches or plaques, localized or widespread, along with tumors, and erythroderma. SS is an inflammatory skin disease with leukemic involvement by malignant T cells. Diagnosis of both MF and SS is made through skin biopsy, blood studies or nodal biopsy.

The TNMB systems is the standard method for staging MF and SS. The TNMB staging is based on evaluation of skin (T), lymph node (N), visceral (M), and blood (B). For MF, early stages (IA to IIA) consist of papules, patches, or plaques, with limited, if any, lymph node involvement and no visceral involvement. Skin-directed therapies can include topical corticosteroids, mechlorethamine, retinoids, imiquimod, localized radiation, or phototherapy (narrowband ultraviolet B [NBUVB] or psoralen plus ultraviolet A [PUVA]).<sup>24</sup> SS Stage IVA1 involves no significant lymph node or visceral involvement, Stage IVA2 is demonstrated by lymph node involvement, but no visceral involvement and Stage IVB includes visceral involvement, with or without nodal involvement. Although no standard initial therapy for patients with SS, systemic therapy can be given alone, with skin directed therapy, or with other systemic therapies.<sup>25</sup>

The NCCN recommends skin-directed therapies as above, used alone or in combination of other skin-directed therapies, dependent upon limited/localized skin involvement or generalized skin involvement.<sup>22</sup>

### Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2022, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

CPT® Codes	Description
96920	Laser treatment for inflammatory skin disease (psoriasis); total area less than 250 sq. cm
96921	Laser treatment for inflammatory skin disease (psoriasis); 250 sq. cm to 500 sq. cm
96922	Laser treatment for inflammatory skin disease (psoriasis); over 500 sq. cm

### ICD-10-CM Diagnosis Codes that Support Coverage Criteria

ICD 10 CM Code	Description
L20.81	Atopic neurodermatitis
L20.82	Flexural eczema
L20.84	Intrinsic (allergic) eczema
L20.89	Other atopic dermatitis
L40.0	Psoriasis vulgaris (plaque psoriasis)

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ICD 10 CM Code	Description
L80	Vitiligo
C84.00	Mycosis fungoides, unspecified site
C84.01	Mycosis fungoides, lymph nodes of head, face, and neck
C84.02	Mycosis fungoides, intrathoracic lymph nodes
C84.03	Mycosis fungoides, intra-abdominal lymph nodes
C84.04	Mycosis fungoides, lymph nodes of axilla and upper limb
C84.05	Mycosis fungoides, lymph nodes of inguinal region and lower limb
C84.06	Mycosis fungoides, intrapelvic lymph nodes
C84.07	Mycosis fungoides, spleen
C84.08	Mycosis fungoides, lymph nodes of multiple sites
C84.09	Mycosis fungoides, extranodal and solid organ sites
C84.10	Sezary disease, unspecified site
C84.11	Sezary disease, lymph nodes of head, face, and neck
C84.12	Sezary disease, intrathoracic lymph nodes
C84.13	Sezary disease, intra-abdominal lymph nodes
C84.14	Sezary disease, lymph nodes of axilla and upper limb
C84.15	Sezary disease, lymph nodes of inguinal region and lower limb
C84.16	Sezary disease, intrapelvic lymph nodes
C84.17	Sezary disease, spleen
C84.18	Sezary disease, lymph nodes of multiple sites
C84.19	Sezary disease, extranodal and solid organ sites

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	07/16	08/16
References reviewed and updated.	07/17	08/17
References reviewed and updated	05/18	06/18
References reviewed and updated. Specialist review.	05/19	06/19
Revised indication from “Mild, moderate, or severe psoriasis with < 10% body surface area (BSA) involvement” to “Localized plaque psoriasis <10% body surface area (BSA) involvement, individual lesions, or with more extensive disease.” Background updated with recent guidelines from AAD. References reviewed and updated.	05/20	06/20
Annual review. “Experimental/investigational” verbiage replaced in policy statement with “evidence is insufficient to draw conclusions.” Replaced all instances of “member” with “member/enrollee.” Coding reviewed. References reviewed and reformatted. Changed “review date” in the header to “date of last revision” and “date” in the revision log header to “revision date.”	06/21	06/21
Annual review. Background updated with no impact to policy statement. Specialist reviewed. References reviewed and updated.	03/22	03/22
Annual review. Added medically necessary indications I.C. atopic dermatitis and I.D. cutaneous T-cell lymphoma. Removed II.B. atopic	03/23	03/23

Reviews, Revisions, and Approvals	Revision Date	Approval Date
dermatitis from insufficient evidence section. Added codes L20.81, L20.82, L20.89, C84.00 through C84.09, and C84.10 through C84.19 to table of ICD-10-CM diagnosis codes that support coverage criteria. References reviewed and updated.		

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### **Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.



The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

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**Note: For Medicaid members/enrollees**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

**Note: For Medicare members/enrollees**, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs LCDs and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

**CLINICAL POLICY**  
**Laser Therapy for Skin Diseases**



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**Policy Name:** Light Treatment and Laser Therapies for Benign Dermatologic Conditions

**Effective Date:** 4/19/2023

## Important Information - Please Read Before Using This Policy

These services may or may not be covered by all Medica plans. Coverage is subject to requirements in applicable federal or state laws. Please refer to the member's plan document for other specific coverage information. If there is a difference between this general information and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid, and other government programs, this policy will apply unless these programs require different coverage. Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions may call the Medica Provider Service Center toll-free at 1-800-458-5512.

Medica coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care, and treatment.

## Coverage Policy

**Note:** This policy is no longer scheduled for routine review of the scientific literature.

**NOTE:** This coverage policy does not address cosmetic indications. Cosmetic procedures are excluded from coverage. Light treatment and laser therapy for dermatologic conditions that are unrelated to an underlying medical condition are considered cosmetic and therefore **NOT COVERED**.

## Light Treatments

1. **Phototherapy** (Ultraviolet A [UVA] and Ultraviolet B [UVB] phototherapies are **COVERED** for the following dermatologic conditions:
  - A. Papulosquamous disorders, such as:
    1. Lichen planus
    2. Pityriasis (e.g., pityriasis rosea; pityriasis rotunda)
    3. Psoriasis (UV-A; UV-B with or without topical coal tar administration)
  - B. Superficial mycoses (e.g., dermatophytosis [ringworm])
  - C. Atopic dermatitis (atopic eczema)
  - D. Prapsoriasis
  - E. Repigmentation of the skin in patients with vitiligo

UVA and UVB phototherapies are investigative and unproven and therefore **NOT COVERED** for all other indications, including but not limited to, treatment of:

- A. Acne vulgaris
- B. Rosacea
- C. Cholestasis of pregnancy
- D. Granuloma annulare
- E. Hydradenitis suppurativa
- F. Lichen simplex chronicus
- G. Morphea (localized scleroderma)
- H. Papular urticaria
- I. Pruritis scleroderma.

There is insufficient reliable evidence in the form of high quality peer-reviewed medical literature to establish the efficacy or effects on health care outcomes.

2. **Photochemotherapy** (psoralen plus UV-A [PUVA]) is **COVERED** for the following dermatologic conditions:

- A. Papulosquamous disorders, such as:
  1. Lichenplanus
  2. Pityriasis (e.g., pityriasis rosea; pityriasis rotunda)
  3. Psoriasis
- B. Superficial mycoses (e.g., dermatophytosis [ringworm])
- C. Atopic dermatitis (atopic eczema)
- D. Prapsoriasis
- E. Repigmentation of the skin in patients with vitiligo

PUVA is investigative and unproven and therefore **NOT COVERED** for all other indications, including but not limited to, treatment of acne vulgaris. There is insufficient reliable evidence in the form of high quality peer-reviewed medical literature to establish the efficacy or effects on health care outcomes.

3. **Photodynamic therapy (PDT)** (e.g., light treatment in conjunction with 5-aminolevulinic acid or methyl aminolevulinate) is **COVERED** for the treatment of actinic keratosis (AK), non-hyperkeratotic.

- A. Actinic keratosis (AK), non-hyperkeratotic

PDT is investigative and unproven and therefore **NOT COVERED** for all other indications, including but not limited to the treatment of acne vulgaris. There is insufficient reliable evidence in the form of high quality peer-reviewed medical literature to establish the efficacy or effects on health care outcomes.

4. **Intense pulsed light phototherapy** is investigative and unproven and therefore **NOT COVERED** for treatment of all benign dermatological indications, including but not limited to:

- A. Papulosquamous disorders, including:
  1. Lichen planus
  2. Pityriasis (e.g., pityriasis rosea; pityriasis rotunda)
- B. Superficial mycoses (e.g., dermatophytosis [ringworm])
- C. Acne vulgaris
- D. Atopic dermatitis (atopic eczema)
- E. Rosacea

There is insufficient reliable evidence in the form of high quality peer-reviewed medical literature to establish the efficacy or effects on health care outcomes.

## **Laser Therapies**

1. **Laser therapy** is **COVERED** for treatment of:

- A. Localized plaque psoriasis
- B. Vitiligo
- C. Atopic dermatitis
- D. Port wine stain (nevus flammeus), including Sturge-Weber syndrome

Laser therapy is investigative and unproven and therefore **NOT COVERED** for all other indications, including but not limited to:

- A. Non-plaque forms of psoriasis
- B. Papulosquamous disorders such as:
  - a. Lichen planus
  - b. Pityriasis rosea (e.g., pityriasis rosea; pityriasis rotunda)
- C. Superficial mycoses (e.g., dermatophytosis [ringworm])
- D. Acne vulgaris
- E. Rosacea
- F. Onychomycosis
- G. Pilonidal sinus disease

There is insufficient reliable evidence in the form of high quality peer-reviewed medical literature to establish the efficacy or effects on health care outcomes.

## Description

The type of light treatment or laser therapy used in dermatology depends upon the type of skin condition or disease being treated, pigmentation, depth, and body surface area involved. Light therapy is most often performed as an outpatient procedure. In addition, home units are also marketed for specified indications. Single or multiple treatments may be administered depending upon the type and severity of skin condition being treated. Therapies addressed in this position statement include the following.

## Ultraviolet (UV) Treatments

**Phototherapy** uses non-ionizing ultraviolet (UV) light to penetrate the surface of the skin in order to slow formation of cells causing dermatologic lesions. Phototherapy has been used to treat atopic dermatitis, eczema, psoriasis, and vitiligo. Most commonly, UVA, broad-band UVB, or narrow-band UVB light is used. UVA lamps deliver light at a wavelength ranging from 320-400 nm, while UVB lamps function at wavelengths in the 290-320 nm range. Narrow-band UVB systems deliver light within a very narrow spectrum peaking between 311 nm and 313 nm. Selection and ongoing monitoring of UV light exposure is important due to increased risk of tissue injury and/or skin cancer.

**Photochemotherapy (PUVA)** involves administration of a phototoxic drug (e.g., Psoralen) along with subsequent exposure to UVA light. Psoralen makes the skin more sensitive to light, thus more responsive to UVA light therapy. Psoralen can be administered orally, applied topically, or in a Psoralen solution waterbath. Similar to phototherapy, photochemotherapy has been used to treat atopic dermatitis, eczema, psoriasis, and vitiligo.

In **photodynamic therapy (PDT)** a photosensitive drug, usually 5-aminolevulinic acid (5-ALA) or methyl aminolevulinate, is administered to the affected area(s) of the skin. The drug passes through the keratin layer overlying the lesion and is metabolized in the underlying tissue to produce concentrations of porphyrin, a powerful photosensitizer. Lesions are subsequently exposed to UV light, which causes activation of the porphyrin. This results in the production of oxygen radicals that destroy the lesion. PDT has been investigated as a treatment of actinic keratoses, as well as other dermatologic lesions.

**Intense pulsed light (IPL)** treatment is application of a high intensity broad-spectrum light administered over a very short time period. It uses special xenon flash lamps and focusing optics to direct the pulsed light to the affected area(s) of the skin. IPL systems target multiple components within cells such as water, melanin, and hemoglobin. The pulses produce selective photothermolysis, which leads to destruction of blood vessels and other structures, while leaving healthy surrounding tissue unaffected. IPL is suggested for: (1) hair removal, (2) treatment of skin imperfections caused by sun damage or aging (e.g., photorejuvenation), and (3) treatment of telangiectatic blood vessels.

## Laser Therapies

Medical lasers can be classified either by (1) the medium used to produce the excited photons, or (2) the characteristic of wavelength administration. Examples of categorization by medium used include:

1. Gas lasers (e.g., carbon dioxide, argon, copper vapor)
2. Solid state lasers (e.g., QS ruby, Neodymium:Yttrium-Aluminum-Garnet [Nd:YAG], Erbium:YAG, KTP [potassium-titanyl-phosphate];)
3. Liquid lasers (dye lasers, pulsed dye lasers)
4. Diode lasers (e.g. injection laser diodes, optically pumped laser diodes)

Examples of categorization by wavelength administration include:

1. Continuous wave lasers (e.g., carbon dioxide; argon)
2. Quasi-continuous wave lasers (e.g., KTP krypton)
3. Pulsed lasers (e.g., pulsed dye; QS ruby; Erbium:YAG; pulsed carbon dioxide).

Two types of laser therapies currently being used for treatment of dermatologic conditions are (1) **excimer lasers** and (2) **pulsed dye lasers**. The **excimer laser** delivers highly coherent, focused UV laser light at a wavelength of

308 nm and has the same mechanism of action as UV phototherapy. Unlike UVB phototherapy, it is localized, thereby focusing on specifically targeted areas and reducing exposure to non-affected areas of the body. Excimer laser therapy has been used for the treatment of psoriasis and vitiligo. **Pulsed dye lasers** emit short pulses of coherent laser light in the infrared to yellow range of the light spectrum, causing the heating of water or oxyhemoglobin in target cells. This heating causes the destruction of the target tissue, or photothermolysis. The short pulses allow for less heat to be produced in the affected cells than is produced with a non-pulsed laser, thereby minimizing injury to adjacent healthy tissue. Pulsed dye laser therapy has been used for the treatment of localized plaque psoriasis.

## FDA Approval

A number of standard **UVA and UVB phototherapy devices** have been approved by the FDA for dermatologic applications, including UVA/UVB lamps used for **photochemotherapy** in association with psoralen administration (PUVA). Various devices are marketed for use within the clinical setting or the home setting. Examples of standard phototherapy devices include, but are not limited to:

1. Houva 4™ System (National Biological)
2. Jordan UVB Light Source (Richmond Light Co. Inc.)
3. LH-75T Phototherapy System (Lerner Medical Devices Inc.)
4. Panosol II® Home Phototherapy Light (National Biological)
5. Resolve™ UVB Phototherapy System (Allux Medical Inc.)

Two **photodynamic therapy systems** (e.g., light treatment in conjunction with 5-aminolevulinic acid or methyl aminolevulinate) have received FDA approval for treatment of nonhyperkeratotic actinic keratosis of the face and scalp:

1. BLU-U™ Blue Light Photodynamic Therapy Illuminator (DUSA Pharmaceuticals) in conjunction with aminolevulinic acid (Levulan®, Kerastick®)
2. PhotoCure Aktilite® CL128 narrowband, red light lamp system, in conjunction with methyl aminolevulinate hydrochloride) cream (Metvixia™)

Several **excimer laser/excimer lamp systems** have been approved by the FDA for UVB phototherapy for specified indications (e.g., psoriasis, vitiligo). Examples of excimer lasers include, but are not limited to:

1. XTRAC® XL Plus Excimer Laser System (PhotoMedex Inc.)
2. PHAROS Excimer Laser EX-308 (RA Medical Systems Inc.)
3. 308 Excimer Lamp Phototherapy system (Quantel Medical Inc.).

Examples of UVB excimer lamps include, but are not limited to:

1. BClear lamp (Lumenis, Inc.)
2. VTRAC® lamp (PhotoMedex Inc.)
3. Excilite™ and Excilite μ™ XeCL lamps (National Biological).

Additional laser systems have been FDA approved for treatment of benign vascular lesions of the face and scalp. These include, but are not limited to:

1. Candela Corp. family of pulsed dye lasers (e.g., C-beam PDL system; V-beam PDL).
2. ClearLight Phototherapy System, Model CL 420 (ClearLight, Ltd.)
3. ClearTouch Intense Pulsed Light System (Radiancy, Inc.)
4. Lumenis Ltd. family of lasers (e.g., Nd: YAG Laser Wavelength [1064 nm]; LightSheer Diode Laser Wavelength [800 nm])
5. PhotoGenica V (Cynosure, Inc.)

## Prior Authorization

Prior authorization is not required. However, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met.

## Coding Considerations

Use the current applicable CPT/HCPCS code(s). The following codes are included below for informational purposes only, and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

### CPT Codes:

- **96567** – Photo dynamic therapy by external application of light to destroy premalignant and/or malignant lesions of the skin and adjacent mucosa (eg, lip) by activation of photosensitive drugs(s), each phototherapy exposure session
- **96900** – Actinotherapy (ultraviolet light)
- **96910** – Photochemotherapy; tar and ultraviolet B (Goeckerman treatment) or petrolatum and ultraviolet B
- **96912** – Photochemotherapy; tar and ultraviolet B (Goeckerman treatment) or petrolatum and ultraviolet B psoralens and ultraviolet A (PUVA)
- **96913** – Photochemotherapy (Goeckerman and /or PUVA) for severe photoresponsive dermatoses requiring at least 4-8 hours of care under direct supervision of the physician (including application of medication and dressings)
- **96920** – Laser treatment for inflammatory skin disease (psoriasis); total area less than 250 sq cm
- **96921** – Laser treatment for inflammatory skin disease (psoriasis); 250 sq cm to 500 sq cm
- **96922** – Laser treatment for inflammatory skin disease (psoriasis); over 500 sq cm

### HCPC Codes:

- **J7308** – Aminolevulinic acid HCL for topical administration, 20%, single unit dosage form (354 mg)
- **J7309** – Methyl aminolevulinate (MAL) for topical administration, 16.8%, 1g
- **J7345** – Aminolevulinic acid HCL for topical administration, 10% gel, 10 mg

Original Policy Effective Date: 3/1/2006

Re-review dates:

- 3/18/2009
- 2/28/2012
- 7/1/2015
- 1/1/2018 – administrative update; codes added
- 4/18/2018
- 2/17/2020 – administrative update; format
- 4/21/2021
- 4/19/2023 – Clinical Review Reserve

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