



# Louisiana

## Laser Treatment of Onychomycosis

**Policy #** 00371

**Original Effective Date:** 07/17/2013

**Current Effective Date:** 08/15/2018

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*Note: Laser Treatment of Acne and Rosacea is addressed separately in medical policy 00162.*

*Note: Laser Treatment of Congenital Port Wine Stain Hemangiomas is addressed separately in medical policy 00166 (Archived 6/17/2009).*

### **Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers laser treatment of onychomycosis to be **investigational**.\*

### **Background/Overview**

#### **ONYCHOMYCOSIS**

Onychomycosis is a common chronic fungal infection of the nail. It is estimated to cause up to 50% of all nail disease and 33% of cutaneous fungal infections. The condition can affect toenails or fingernails but is more frequently found in toenails. Primary infectious agents include dermatophytes (e.g., *Trichophyton* species), yeasts (e.g., *Candida albicans*), and nondermatophytic molds. In temperate Western countries, infections are generally caused by dermatophytes.

Aging is the most common risk factor for onychomycosis, most likely due to decreased blood circulation, longer exposure to fungi, and slower nail growth. Also, various medical conditions increase the risk of comorbid onychomycosis. They include diabetes, obesity, peripheral vascular disease, immunosuppression, and human immunodeficiency virus (HIV) infection. In certain populations, onychomycosis may lead to additional health problems. Although there is limited evidence of a causal link between onychomycosis and diabetic foot ulcers, at least 1 prospective study with diabetic patients found onychomycosis to be an independent predictor of foot ulcer. Moreover, onychomycosis, especially more severe cases, may adversely impact the quality of life. Patients with onychomycosis have reported pain, uncomfortable nail pressure, embarrassment, and discomfort wearing shoes.

### **Diagnosis**

The diagnosis of onychomycosis can be confirmed by potassium hydroxide preparation, culture, or histology.

### **Treatment**

Treatments for onychomycosis include topical antifungals such as nail paints containing ciclopirox (ciclopiroxolamine) or amorolfine and oral antifungals such as terbinafine and itraconazole. These have low-to-moderate efficacy and a high relapse rate. Topical antifungals and some long-available oral medications

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(e.g., griseofulvin) require a long course of treatment, which presents issues for patient compliance. Moreover, oral antifungal medications have been associated with adverse effects such as a risk of hepatotoxicity.

Several types of device-based therapies are under investigation for the treatment of onychomycosis, including ultrasound, iontophoresis, photodynamic therapy, and laser systems. A potential advantage of lasers is that they have greater tissue penetration than antifungal medication and thus may be more effective at treating infection embedded within the nail. Another potential advantage is that laser treatments are provided in a clinical setting in only one or several sessions and, thus, requires less long-term patient compliance.

Laser treatment of onychomycosis uses the principle of selective photothermolysis. This is defined as the precise targeting of tissue using a specific wavelength of light. The premise is that light is absorbed into the target area and heat generated by that energy is sufficient to damage the target area while sparing the surrounding area. The aim of laser treatment for onychomycosis is to heat the nail bed to temperatures required to disrupt fungal growth (approximately 40°-60°C) and at the same time avoid pain and necrosis to surrounding tissues.

Characteristics of laser systems used to treat onychomycosis are listed in Table 1.

**Table 1. Characteristics of Lasers for Treating Onychomycosis**

Variables	Characteristics
Wavelength	Lasers are single-wavelength light sources. There needs to be sufficient tissue penetration to adequately treat nail fungus. The near-infrared spectrum tends to be used because this part of the spectrum has maximum tissue penetrance in the dermis and epidermis and the nail plate is similar to the epidermis. To date, most laser systems for treating onychomycosis have been Neodymium yttrium aluminum garnet (Nd:YAG) lasers that typically operate at 1064 nm; 940- to 1320-nm and 1440-nm wavelengths are also options.
Pulse duration	Pulses need to be short to avoid damaging the tissue surrounding the target area. For example, short-pulse systems have microsecond pulse durations and Q-switched lasers have nanosecond pulse durations.
Repetition rate (frequency of pulses, in hertz)	Spot size to the diameter of the laser beam. For treating onychomycosis, laser spot sizes range from 1 to 10 mm.
Fluence (in J/cm <sup>2</sup> )	Fluence refers to the amount of energy delivered into the area

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

Multiple neodymium yttrium aluminum garnet (Nd:YAG) laser systems have been cleared by the U.S. FDA for marketing for the temporary increase of clear nail in patients with onychomycosis. The FDA has determined that these devices were substantially equivalent to existing devices. Table 2 lists select approved laser systems.

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**Table 2. Select Laser Systems Approved for Temporary Increase of Clear Nail in Patients With Onychomycosis**

Device	Manufacturer	Approved
<b>Nd:YAG 1064-nm laser systems</b>		
PinPointe™‡ FootLaser™‡	PinPointe USA (acquired by NuvoLase 2011)	2010
GenesisPlus™‡	Cutera	2011
VariaBreeze™‡	CoolTouch	2011
JOULE ClearSense™‡	Sciton	2011
GentleMax Family of Laser Systems	Candela	2014
Nordlys	Ellipse A/S	2016
<b>Dual wavelength Nd:YAG 1064-nm and 532-nm laser system</b>		
Q-Clear™‡	Light Age	2011

Nd:YAG 1064-nm laser systems (FDA product code: GEX); dual-wavelength Nd:YAG 1064-nm and 532-nm laser system (FDA product code: PDX).

### Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

### Rationale/Source

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The main question for this evidence review is whether laser treatment is an efficacious treatment for onychomycosis and whether it is at least as effective as alternatives. RCTs with appropriate comparison groups are the best study design to evaluate the effectiveness of laser treatment for onychomycosis. The

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most important outcomes for onychomycosis treatments are the clinical cure of onychomycosis (i.e., complete clearing without recurrence) and mycologic cure. Other useful outcomes would be symptoms and functional measures related to onychomycosis. Partial healing and accelerated nail growth are intermediate outcomes that may or may not be associated with the ultimate cure rate. The most appropriate comparator interventions are sham laser treatment if patient blinding is considered necessary, and best alternative care (e.g., topical antifungals).

### **LASER TREATMENT FOR ONYCHOMYCOSIS**

#### **Systematic Reviews**

A 2014 systematic review by Bristow identified 12 published studies on laser treatment for onychomycosis. Two were RCTs, four were nonrandomized comparative studies, and the other six were case series. Bristow did not pool study findings but concluded that the evidence was limited and of poor methodologic quality.

Representative RCTs with the largest sample sizes that compared laser treatment with placebo or with a different intervention are described next.

#### **Randomized Controlled Trials**

Karsai et al (2017) reported on a prospective randomized pilot trial with blinded outcome assessment comparing laser treatment (short-pulsed 1064-nm-ND:YAG laser) with control (no laser treatment) in 20 patients with 82 mycotic toenails. All patients received treatment with amorolfine cream over the soles of the feet, their intertriginous areas, and the skin directly surrounding the nails. Patients in the laser group received 4 treatments at intervals of 4 to 6 weeks. The trial's primary end point (the proportion of nails with mycologic remission) was not achieved in either group after 12 months. The trial's secondary end point was the clinical appearance of the nails using the Onychomycosis Severity Index (OSI), which was assessed by 2 independent blinded investigators. There were no differences in OSI scores at baseline or at 12-month follow-up. The OSI score worsened by a mean of 2.0 points in the treatment group compared with 3.6 points in the control group (between group change, 1.6 points; 95% confidence interval, -0.7 to 3.9;  $p=0.553$ ).

In another RCT, Kim et al (2016) compared 1064-nm Nd:YAG laser therapy alone ( $n=19$ ) with laser using topical antifungal therapy ( $n=18$ ) and topical antifungal therapy ( $n=19$ ) among 56 patients (in the final group; original N enrolled not specified). Topical antifungal therapy included naftifine spray. Laser sessions were repeated at 4-week intervals for 12 weeks. Clinical response rates at 12 weeks were 70.9% in the laser only group, 73.2% in the laser plus topical group, and 14.9% in the topical group ( $p<0.05$  for difference vs topical-only group). Cure rates at 24 weeks were 15.2% in the laser only group, 22.5% of the laser plus topical group, and 4.5% of the topical group ( $p<0.05$  for difference vs topical-only group). There was no mention of blinded outcome assessment.

In 2015, El-Tatawy et al in Egypt reported on 40 patients with toenail onychomycosis randomized to 4 sessions of treatment with a 1064-nm Nd:YAG laser ( $n=20$ ) or topical terbinafine twice daily for 6 months ( $n=20$ ). The laser was a Dualis SP device (Fotona, Slovenia). The clinical efficacy outcome measure

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categorized patients into those with marked improvement (>75%), moderate improvement (50%-75%), mild improvement (25%-50%), or no improvement (<25%). The authors did not state whether the outcome assessment was blinded. At the end of the 6 months, 100% of patients in the laser group and none in the medication group showed marked improvement ( $p<0.002$ ). In the medication group, 8 patients had mild improvement, two had moderate improvement, and ten had no improvement. Lack of blinding could have introduced bias in the clinical assessment of patients.

A 2014 trial by Xu et al in China randomized 53 patients with toenail onychomycosis to 1 of 3 treatment groups: daily oral terbinafine 250 mg, weekly long-pulsed 1064-nm Nd:YAG laser (Luminis One), or a combination of both therapies. The medication-only group included 16 patients with 30 infected nails, the laser group included 18 patients with 31 infected nails, and the combination treatment group included 16 patients with 29 infected nails. The analysis was done on a per-nail basis. All patients completed the 24-month follow-up. At this final evaluation point, the clinical clearance rate (defined as  $\leq 5\%$  nail plate involvement in onychomycosis) was 22 (73.3%) of 30 nails in the medication-only group, 20 (64.5%) of 31 nails in the laser group, and 28 (96.6%) of 29 nails in the combination treatment group. The rate was significantly higher in the combined treatment group than in either treatment alone; clinical clearance in the medication vs laser group did not differ significantly. Findings were similar for the mycological clearance rate. A trial limitation was its reporting of outcomes on a per-nail basis, which did not account for correlated measurements.

In 2010, an industry-sponsored study by Landsman et al used a dual-wavelength near-infrared diode laser that has not been cleared by the U.S. FDA for treatment of onychomycosis. The trial included 36 patients with mycologically confirmed onychomycosis. Patients were randomized to actual laser treatment ( $n=26$ ) or sham treatment ( $n=10$ ). The sham treatment group received the same number of sessions, but laser power was set to zero. Thirty-four (94%) of 36 patients completed the study. These 34 patients had a total of 59 toes treated with an active or sham laser. Thirty-seven toes met all of the clinical eligibility criteria (26 in the active treatment group, 11 in the control group).

The primary study outcomes were the proportion of patients who had at least 3 mm of clear nail growth and who attained a negative mycologic finding. As assessed by the blinded expert panel, at 180 days, 17 (65%) of 26 toes in the active treatment group and 1 (9%) of 11 in the control group attained at least 3 mm of clear lineal nail growth. The difference between groups was statistically significant, favoring the active treatment group ( $p=0.011$ ). Moreover, 10 (39%) of 26 toes in the active treatment group and 1 (9%) of 11 in the control group had both a negative mycologic culture and at least 3 mm of clear nail growth at 180 days; the difference between groups was not statistically significant ( $p=0.119$ ).

In the subjective clinical visual assessment of improvement at 180 days, investigators judged 5 (19%) of 26 toes in the active treatment group and 2 (18%) of 11 in the control group to be markedly improved. No toes were judged to be completely cleared. After reviewing photographs, the expert panel judged 1 (4%) toe in the active treatment group and 2 (18%) toes in the control group to be markedly improved and 1 toe (4%) in the active treatment group to be completely cleared. (Statistical comparisons of the treatment vs sham group were not reported for the visual assessment outcome.)

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In 2012, Landsman and Robbins reported 270-day results in 36 of 40 treated toes. (This included clinically eligible toes as well as companion toes.) When photographs of 34 toes were evaluated, 35% were considered to have continued improvement, 38% were considered not to have changed since 180 days, and 20% were considered to have worsened. Authors did not report 270-day findings for patients assigned to the sham control group.

Limitations of the 2 Landsman studies included the intermediate outcome measures used (e.g., 3 mm of clear lineal nail growth), which are of uncertain clinical significance. Also, investigators randomized patients to a treatment group and a control group yet presented their findings on a per-*nail* basis, which did not account for correlated measurements. Three (9%) of the 34 patients evaluated at 180 days contributed data from 2 toes to the analysis.

### SUMMARY OF EVIDENCE

For individuals who have onychomycosis who receive treatment with laser therapy, the evidence includes small RCTs. Relevant outcomes are symptoms, change in disease status, medication use, and treatment-related morbidity. Some of the available randomized controlled trials have reported improvements in clinical outcomes with laser treatment, but these trials have mixed results and methodologic limitations. Clinical and mycologic outcomes sometimes differed in the trials, which may be due in part to lack of consistent blinding of outcome assessment. The published evidence to date does not permit determining whether laser treatment improves health outcomes in patients with onychomycosis. Additional well-designed, adequately powered, and well-conducted randomized controlled trials are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

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### **Policy History**

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Current Effective Date:	08/15/2018
06/27/2013	Medical Policy Committee review
07/17/2013	Medical Policy Implementation Committee approval.
07/10/2014	Medical Policy Committee review
07/16/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date:	08/2019

### **Coding**

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	17999, 96999
HCPCS	No codes
ICD-10 Diagnosis	B35.1

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
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