

2.01.89	Laser Treatment of Onychomycosis		
Original Policy Date:	December 4, 2015	Effective Date:	February 1, 2020
Section:	2.0 Medicine	Page:	Page 1 of 8

Policy Statement

Laser treatment of onychomycosis is considered **investigational**.

Policy Guidelines

There is no specific CPT code for this treatment. It would likely be reported using the unlisted CPT codes:

- **17999:** Unlisted procedure, skin, mucous membrane and subcutaneous tissue
- **96999:** Unlisted special dermatological service or procedure

Description

Onychomycosis is a common fungal infection of the nail. Currently available treatments for onychomycosis, including systemic and topical antifungal medications, have relatively low efficacy and require a long course of treatment. Laser systems are proposed as another treatment option.

Related Policies

- Nonpharmacologic Treatment of Rosacea

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Multiple Nd:YAG laser systems have been cleared by the U.S. Food and Drug Administration (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 1 lists select approved laser systems.

Table 1. Select Laser Systems Approved for Temporary Increase of Clear Nail in Patients with Onychomycosis

Device	Manufacturer	Approved
Nd:YAG 1064-nm laser systems		
PinPointe™ FootLaser™	PinPointe USA (acquired by NuvoLase 2011)	2010
GenesisPlus™	Cutera	2011
VariaBreeze™	CoolTouch	2011
JOULE ClearSense™	Sciton	2011

Device	Manufacturer	Approved
GentleMax Family of Laser Systems	Candela	2014
Nordlys	Ellipse A/S	2016
Dual-wavelength Nd:YAG 1064-nm and 532-nm laser system		
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).		

Rationale

Background

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.¹ 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 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 one prospective study with diabetic patients found onychomycosis to be an independent predictor of foot ulcers.² 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.^{3,4}

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 (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, require less long-term patient compliance.

Laser treatment of onychomycosis uses the principle of selective photothermolysis, 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.⁵

Characteristics of laser systems used to treat onychomycosis are listed in Table 2.⁵

Table 2. 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 ²)	Fluence refers to the amount of energy delivered into the area

Literature Review

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

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

Laser Treatment for Onychomycosis

Clinical Context and Therapy Purpose

The purpose of laser treatment in patients who have onychomycosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of laser treatment improve the net health outcome compared with topical antifungal nail lacquer or oral antifungal therapy in patients who have onychomycosis?

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

Patients

The relevant population of interest are patients with onychomycosis.

Interventions

The therapy being considered is laser treatment. Laser treatment allows for precise targeting of the fungal areas with enough heat to disrupt growth while avoiding damage to surrounding

tissues. Two types of lasers have been developed to treat onychomycosis: neodymium-doped:yttrium aluminum garnet (Nd:YAG) and diode lasers.

Laser treatments are performed in outpatient centers.

Comparators

Current treatments for onychomycosis include topical antifungal nail lacquer and oral antifungal therapy. These treatments typically require long courses, which result in poor patient compliance and high relapse rates. Nail lacquers contain ciclopirox or amorolfine. Oral medications are terbinafine and itraconazole, which have been associated with a risk of hepatotoxicity.

Outcomes

The general outcomes of interest are symptom relief (e.g., clear nail growth), change in disease status (e.g., mycologic remission or Onychomycosis Severity Scale scores), reduction in medication use, and treatment-related morbidity.

Clinical response can be measured after laser treatment (three-six months). To determine remission rates, follow-up may last a year or more.

Study Selection Criteria

To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

Systematic Reviews

A systematic review by Bristow et al (2014) identified 12 published studies on laser treatment for onychomycosis in a literature search conducted in June 2014.⁶ Two were RCTs, four were nonrandomized comparative studies with no placebo or control group, and six were case series. Bristow et al (2014) did not pool study findings, concluding the evidence was limited and of poor methodologic quality.

Randomized Controlled Trials

Representative RCTs published after the systematic review, with the largest sample sizes, and comparing laser treatment with placebo or a different intervention are described next.

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.⁷ 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 four treatments at intervals of four to six weeks. The trial's primary endpoint (the proportion of nails with mycologic remission) was not achieved in either group after 12 months. The trial's secondary endpoint was the clinical appearance of the nails using the Onychomycosis Severity Index, which was assessed by two independent blinded investigators. There were no differences in Onychomycosis Severity Index scores at baseline or at 12-month follow-up. The Onychomycosis Severity Index 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; $p=0.553$).

Kim et al (2016) compared 1064-nm Nd:YAG laser therapy alone ($n=19$) with a laser plus topical antifungal therapy ($n=18$) and topical antifungal therapy alone ($n=19$) (in the final group; original N enrolled not specified) for 12 weeks.⁸ 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 alone group ($p<0.05$ for laser and laser plus topical groups 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 laser and laser plus topical groups vs topical-only group). There was no mention of blinded outcome assessment.

El-Tatawy et al (2015) 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).⁹ The laser was a Dualis SP device (Fotona). The clinical efficacy outcome measure categorized patients into those with a 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 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, eight 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.

Xu et al (2014) in China randomized 53 patients with toenail onychomycosis to 1 of 3 treatment groups: daily oral terbinafine 250 mg (16 patients, 30 nails), weekly long-pulsed 1064-nm Nd:YAG laser (Luminis One) (18 patients, 31 nails), or a combination of both therapies (n=16 patients, 29 nails).¹⁰ 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.

An industry-sponsored study by Landsman et al (2010) used a dual-wavelength near-infrared diode laser that has not been cleared by the U.S. Food and Drug Administration for treatment of onychomycosis.¹¹ 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 linear nail growth. The difference between groups was statistically significant, favoring the active treatment group ($p=0.011$). Ten (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 ($p=0.119$). Differences between these two outcomes might be attributed to the subjective nature of the visual assessments.

Landsman and Robbins (2012) reported 270-day results in 36 of 40 treated toes.¹² (This included clinically eligible toes as well as companion toes.) When photographs of 34 toes were evaluated, 35% were considered to have continuous improvement, 38% were considered not to have changed for 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 and Robbins (2012) studies included the intermediate outcome measures used (e.g., 3 mm of clear linear 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, randomized controlled trials. The relevant outcomes are symptoms, change in disease status, medication use, and treatment-related morbidity. The randomized controlled trials reported inconsistent results and had methodologic limitations. Clinical and mycologic outcomes differed across the trials, lacked consistent blinding of outcome assessments, and often reported outcomes on a per-nail basis without accounting for correlated measurements. 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.

Supplemental Information

Practice Guidelines and Position Statements

British Association of Dermatologists

The British Association of Dermatologists (2014) issued guidelines on the management of onychomycosis.¹³ Due to the limited nature of the evidence, the Association concluded that “lasers are showing promising results in the treatment of onychomycosis, but recommendations cannot be made at this stage” (level of evidence 1-).

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02812043	Comparison Between Long-pulsed Nd:YAG, Amorolfine and Combination Treatment in Treating Non-dermatophyte Onychomycosis	60	Aug 2018* (ongoing)
NCT02019446	Laser Treatment for Onychomycosis in Diabetes	60	Dec 2021
Unpublished			
NCT01996995	Laser Therapy for Onychomycosis in Patients with Diabetes at Risk for Diabetic Foot Complications (LASER-1)	64	Jul 2017 (completed)
NCT01915355	Pulsed Dye Laser Treatment of Onychomycosis	11	Jul 2015 (completed)

NCT: national clinical trial; Nd:YAG: neodymium yttrium aluminum garnet.

^a Denotes industry-sponsored or cosponsored trial.

* No results published as of October 2019

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12. Landsman AS, Robbins AH. Treatment of mild, moderate, and severe onychomycosis using 870- and 930-nm light exposure: some follow-up observations at 270 days. J Am Podiatr Med Assoc. Mar-Apr 2012;102(2):169- 171. PMID 22461276
13. Ameen M, Lear JT, Madan V, et al. British Association of Dermatologists' guidelines for the management of onychomycosis 2014. Br J Dermatol. Nov 2014;171(5):937-958. PMID 25409999
14. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 2.01.89 (December 2019).

Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE

The following services may be considered investigational.

Type	Code	Description
CPT®	17999	Unlisted procedure, skin, mucous membrane and subcutaneous tissue
	96999	Unlisted special dermatological service or procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
12/04/2015	BCBSA Medical Policy Adoption
02/01/2017	Policy revision without position change
02/01/2018	Policy revision without position change
02/01/2019	Policy revision without position change
02/01/2020	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.