Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 1/1/23**
(See policy history boxes for previous effective dates)

Title: Polymerase Chain Reaction (PCR) Testing in the Diagnosis of Onychomycosis

Description/Background

Classically, onychomycosis diagnosis has been performed by a combination of microscopic approaches and “in vitro” cultures. These 2 methods have limitations. Indeed, direct microscopic examination can only confirm a fungal infection, without genus or species identification of the causative agent. Cultures are slow and false negative results have been reported in up to 40% of positive direct microscopic examination cases. False-positives have also resulted due to saprophytic and environmental mould contamination.

Polymerase chain reaction (PCR) assays have been developed to detect fungal DNA from infected nails. PCR is a technique that permits the amplification of very short sections of DNA (or RNA) into very large numbers of the same sequence. Thousands to millions of copies of a particular DNA (or RNA) sequence can be generated, allowing for identification of dermatophytes and nondermatophytes in just a few hours.

Onychomycosis (toenail fungus) is a fungal infection of one or more units of the nail caused by dermatophytes, or mould and nondermatophytes yeast. In 2013, as part of the Choosing Wisely® initiative from the American Board of Internal Medicine Foundation, the American Academy of Dermatology released recommendations that cautioned against prescribing oral antifungal therapy for suspected nail fungus prior to diagnostic confirmation of fungal infection. The American Academy of Dermatology concluded that about half of suspected fungal infections are not fungal infections and starting patients on treatment before confirming diagnosis could unnecessarily expose them to the adverse effects of antifungal therapy.(1)

Current Gold Standard - Direct Microscopy and Culture Confirmation
Microscopic examination with 20% potassium hydroxide (KOH) is useful for ruling out the presence of fungi. Direct microscopy cannot identify the specific pathogen if fungi is present. A fungal culture is then used to amplify DNA by cloning the segments of interest into vectors for expression in bacteria and identify the species of organism. This process takes weeks, but organism identification is vital in the treatment as optimal therapy varies with the pathogen identified. Nondermatophyte molds may be resistant to the conventional therapy used for the more common dermatophytes.(2)

Regulatory Status

N/A

Medical Policy Statement

Polymerase chain reaction for the diagnosis of onychomycosis is experimental/ investigational. There is insufficient scientific evidence in the current medical literature to indicate that this technology is as beneficial as the established alternatives.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

N/A

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:

N/A

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

81400	81401	81402	81403	81404	81405
81406	81407	81479	87798	87801	

Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

Onychomycosis represents one of the most frequent mycoses in the world. Causative agents are mainly dermatophytes, but yeasts and nondermatophyte moulds can also be involved. Conventional diagnostic methods include direct microscopy (or histology) and culturing.

Cuchi-Burgos et al (2020) evaluated the clinical utility of incorporating a clinical laboratory workflow of commercial real time PCR for dermatophytes detection in nails. One hundred and fifty-two nail samples were included (34 KOH negative and 118 KOH positive) and processed by culture and qPCR. In the negative KOH group, only one dermatophyte grew in culture and 3 were detected by qPCR. In the group of positive KOH, 57 dermatophytes grew in culture and 81 were detected by qPCR. In this group, 25% of diagnosed dermatophytes were detected only by qPCR. Although the sensitivity of qPCR compared to culture is 92.8% and time of response decreases from days to hours, qPCR testing has not proven to be better than the standard of care with direct microscopy and culture mediums.

Lubis et al (2018) evaluated the diagnostic value of Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) in the diagnosis of onychomycosis using fungal culture as the gold standard. Onychomycosis consist of three groups: (1) dermatophytes (include: *Trichophyton rubrum, Trichophyton mentagrophytes*, and *Epidermophyton floccosum)*, (2) non-dermatophytes/mould (include *Acremonium sp., Alternaria sp., Aspergillus sp., Botryodiplodia theobromae, and Fusarium sp., etc.)* and (3) Candida albicans (most commonly found yeast). Twenty-five nail samples were taken from a single institution and divided into 2 envelops. The first was taken to the microbiology lab for the fungal culture and the second was taken to the integrated laboratory for the PCR-RFLP. Upon comparison of the culture to the PCR-RFLP, sensitivity and specificity of PCR-RFLP yielded a specificity value of 85.71% and a sensitivity value of 28.71%. The authors concluded that even though the numbers are lower with PCR-RFLP, the invasiveness of Periodic acid Schiff-staining compared to PCR-RFLP method should be taken into consideration.

Hafirassou et al (2017) assessed the usefulness of different real time PCR (RT-PCR) assays for identifying species causing onychomycosis in samples from 70 patients and 15 controls. Conventional methods and 4 different RT-PCR assays were used: a panfungal, a pandermatophyte and 2 specific assays for detecting Candida spp. and Aspergillus spp. Fungal elements were visualized in 58% of the samples, and 54% of cultures were positive. Panfungal and pandermatophyte RT-PCR were positive in 28% and 60%, respectively, and the sensitivity relative to positive cultures was 47% and 90%. Candida spp. were detected in 76% of samples analyzed and Aspergillus spp. in 60%. These species were also present in 80% of control cases. The authors concluded that molecular techniques were useful but showed limitations. The panfungal assay showed a low sensitivity, the pandermatophyte assay was sensitive and specific but did not allow for differentiation among species of dermatophytes. Finally, the role of non-dermatophyte species detected by using specific RT-PCR techniques should be carefully analyzed as these species were also present in healthy nails. Molecular techniques assessed in this study were useful but limitations should be taken into consideration.

Summary of Evidence:
Conventional onychomycosis diagnostic methods have several limitations such as time-cost, low sensitivity and the need for skilled personnel. However, no PCR kits testing for onychomycosis have been FDA approved and results appear to vary from kit to kit. Molecluar methods appear to hold promise to achieve a rapid diagnosis. Further research, to compare PCR testing to current standard of care techniques, is needed to determine clinical utility and whether this technology improves health outcomes over conventional methods.

Supplemental Information

POSITION STATEMENTS AND GUIDELINES
The American Academy of Dermatology (2013) published a recommendation encouraging the confirmation of fungal infection prior to prescribing antifungal therapy. Side effects of therapy want to be avoided when appropriate. No recommendation was made regarding the type of testing that should be used for confirmation.

Government Regulations
National:
There is no national coverage determination on this testing.

Local:
There is no local coverage determination on this testing.

(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.)

Related Policies

N/A

References

1. [Guideline] American Academy of Dermatology. Ten Things Physicians and Patients Should Question. Choosing Wisely. October 29, 2013; http://www.choosingwisely.org/societies/american-academy-of-dermatology/. Accessed August 29, 2022.
2. Cuchí-Burgos E, Rubio-Casino R, Ballestero-Téllez M, Pariente-Jiménez F, Pérez-Jové J, Blanco-Suárez A. Commercial real time PCR implementation for rapid diagnosis of onychomycosis: A new workflow in a clinical laboratory [published online ahead of print, 2020 Jul 15]. Enferm Infec Microbiol Clin. 2020;S0213-005X(20)30231-7.
3. Elewski BE. Clinical pearl: diagnosis of onychomycosis. *J Am Acad Dermatol*. 1995 Mar. 32(3):500-1.
4. Hafirassou AZ, Valero CI, Gassem N, Mihoubi I, Buitrago MJ. Usefulness of techniques based on real time PCR for the identification of onychomycosis-causing species. Mycoses. 2017;60:638–644. https://doi.org/10.1111/myc.12629
5. Hayette M.P., Seidel, L., et al., Clinical evaluation of the DermaGenius® Nail real time PCR assay for the detection of dermatophytes and Candida ablicans in nails. Medical Mycology. May 2018. doi:10.1093/mmy/myy020.
6. Lubis NZ, Muis K, Nasution LH. Polymerase Chain Reaction-Restriction Fragment Length Polymorphism as a Confirmatory Test for Onychomycosis. Open Access Macedonian Journal of Medical Sciences. 2018;6(2):280-283. doi:10.3889/oamjms.2018.098.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 8/29/22, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/19	10/16/18	10/16/18	Joint policy established
1/1/20	10/15/19		Routine maintenance
1/1/21	10/20/20		Routine maintenance
1/1/22	10/19/21		Routine maintenance
1/1/23	10/18/22		Routine maintenance (slp)

Next Review Date: 4th Qtr, 2023

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: POLYMERASE CHAIN REACTION (PCR) TESTING IN THE DIAGNOSIS OF ONYCHOMYCOSIS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	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.