Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 1/1/25**
(See policy history boxes for previous effective dates)

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

Description/Background

Polymerase Chain Reaction (PCR) assays, are a lab technique that may identify resistant organism(s) (fungal, bacterial, or viral) which cause onychomycosis. Small quantities of DNA or RNA in a sample are amplified and detected using a targeted approach. Very short sections of DNA (or RNA) are copied into very large numbers to generate thousands to millions of copies of a particular DNA (or RNA) sequence, which allows for identification of dermatophytes and non-dermatophytes in just a few hours. Specification of the pathogenic fungi is beneficial when making decisions associated with anti-fungal therapy as different organisms respond differently to various antifungal medications.

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.

Onychomycosis (toenail fungus) is a fungal infection of 1 or more units of the nail caused by dermatophytes, or mould and non-dermatophytes yeast. The American Academy of Dermatology (2013) indicates that about half of suspected fungal infections are not fungal infections and starting individuals on treatment before confirming diagnosis could unnecessarily expose them to the adverse effects of antifungal therapy. Therefore, 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.(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. Non-dermatophyte molds may be resistant to the conventional therapy used for the more common dermatophytes.(3)

Regulatory Status

N/A

Medical Policy Statement

The effectiveness and clinical utility of polymerase chain reaction testing for onychomycosis has been established. It may be considered a useful therapeutic option when criteria are met.

Inclusionary and Exclusionary Guidelines

Inclusions:
Polymerase chain reaction testing when **BOTH** of the following are met:

- Conventional testing (e.g. microscopy, KOH test, PAS stain, culture) has confirmed the presence of onychomycosis
- Anti-fungal therapy has failed to resolve the infection

Exclusions:
Polymerase chain reaction testing in all other situations not meeting the criteria above.

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:

81400	81401	81402	81403	81404	81405
81406	81407	81479	87798	87801	

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

N/A

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 1 of the most frequent mycoses in the world. Causative agents are mainly dermatophytes, but yeasts and non-dermatophyte moulds can also be involved. The major diagnostic tests for onychomycosis include KOH preparations, histopathologic examination of nail clippings with a PAS stain, fungal culture, and PCR assays.

Goldstein et al (2024; Up-To-Date) discussed the different methods and listed the strengths and weakness of the various testing methods.

- A potassium hydroxide (KOH) preparation provides almost immediate results. The sensitivity has been reported as 67 to 97 percent but is dependent on factors such as specimen adequacy and clinician experience. The specificity range has been reported as 38 to 78 percent but may increase with repletion of the test. It may also be enhanced through use of a stain. The technique for obtaining the specimen is critical and sample should be taken from the most proximal accessible region. The KOH test does not provide specifics on the pathogen or assess fungus viability.
- Histopathology is easy to perform and identifies fungal elements with high sensitivity. Results are generally available within a few days if access to pathology services is readily available. PAS stain evaluation was found to be higher in cost than KOH preparation. One study indicated that the PAS stain is a more sensitive test than culture or KOH examination (82%, 53%, and 48%). This technique is less favorable than others because it requires a biopsy of the nail plate or partial or full nail removal. Histopathology does not provide specifics on the pathogen or assess fungus viability.
- Fungal cultures allow for both identification and specification of the pathogen involved. Specificity is reported at 83 to 100 percent, however the sensitivity is 31 to 59 percent). Results may take a few weeks and about one-third of cultures are falsely negative, which requires the need for repeat or other testing when there is a strong suspicion of onychomycosis. Cultures occasionally demonstrate non-dermatophyte molds which may indicate a true reading or could be a result of contamination.
- Polymerase chain reaction is generally available in 1 to 2 days and provides a way to detect both fungal DNA and identify the type of pathogen present. However, availability and cost have been identified as limiting access in some settings. PCR tests vary depending on the manufacturer and the clinicians familiarity with sensitivity, specificity and other limitations of the specific PCR are essential for proper use and interpretation of results. Some tests are only able to assess for dermatophyte infections, whereas others assess broader categories of fungi. In addition, because PCR tests detect DNA, nonviable fungi may be detected.
- Dermatophyte test medium (DTM) culture is cheaper than culture on Sabouraud's medium, can be performed in the clinician's office. Results are available within 3 to 7 days. A disadvantage is the limitation of use for the diagnosis of dermatophyte onychomycosis. It is important to read DTM cultures in a timely fashion and DTM cannot identify the specific pathogen, however such identification is not necessary since all dermatophytes are susceptible to similar therapies. DTM cultures have shown good positive and negative correlation with culture on Sabouraud’s medium.

- Fluorescence microscopy can be used alone or in conjunction with preceding exposure of the clippings to KOH. Sensitive has shown to be more sensitive than KOH preparation or culture (92 versus 80 and 59 percent, respectively).
- Emerging diagnostic methods include an immunochromatographic strip test and reflectance confocal microscopy

Goldstein et al (2024; Up-To-Date) defines the preferred approach as beginning with KOH preparation for any suspected onychomycosis given the rapid availability of results, low cost and ease of the procedure. If the KOH preparation is negative, a histopathologic examination with a PAS stain is recommended. In the event of a positive test a fungal culture to identify the specific pathogen is suggested.

Navarro-Perez et al (2023) investigated the prevalence of onychomycosis, analyze the most appropriate diagnostic test, and assessed the distribution of pathogens based on age, sex, quarter of the year, duration of symptoms and previous treatment. Mycological culture, PCR data and results were retrospectively collected (n=121). Of the 121 samples, 57% (69/121) tested positive when both microbiological study techniques were combined. The prevalence of onychomycosis was higher when PCR was performed (52.1%) compared to microbiological culture (33.1%). Among the 81 samples negative by microbiological culture, 31 were positive by PCR. Similarly, of the 58 samples negative by PCR, 8 were positive by microbiological culture. Diagnostic accuracy data (with 95% confidence intervals) for PCR, using microbiological culture as the gold standard, were as follows: sensitivity of 0.8, specificity of 0.62, positive predictive value of 0.51 and negative predictive value of 0.86. Authors concluded that combining microbiological culture and PCR can increase the detection rate of onychomycosis and help avoid false-negative results.

Caldwell et al (2020) compared commercial multiplex PCR against Periodic Acid–Schiff (PAF) testing for the diagnosis of onychomycosis. Proximal samples of the affected toenail and subungual debris were obtained from each individual who was clinically diagnosed with onychomycosis (n=203). The samples were split into 2 equal parts. One part was sent for multiplex PCR testing and the other for PAS testing. One-hundred and nine samples (53.7%) tested positive with PAS, 77 samples (37.9%) tested positive with PCR. Forty-one patients tested positive with PAS but negative with PCR, and 9 tested positive with PCR but negative with PAS. The McNemar test showed that the proportion of positive results from PAS analysis was significantly greater than that for PCR analysis ($p < 0.0005$).The authors conclude that PAS remains the best initial test compared with PCR in detecting onychomycosis in a nail sample from an individual who demonstrates clinical evidence of a fungal nail infection. However, multiplex PCR testing may be a useful tool when PAS testing has failed to provide effective treatment.

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 PCR. In the negative KOH group, only 1 dermatophyte grew in culture and 3 were detected by PCR. In the group of positive KOH, 57 dermatophytes grew in culture and 81 were detected by PCR. In this group, 25% of diagnosed dermatophytes were detected only by PCR. Although the sensitivity of PCR compared to culture is 92.8% and time of response decreases from days to hours.

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 species were detected in 76% of samples analyzed and Aspergillus species 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:
The most common conventional laboratory diagnosis of onychomycosis involves direct microscopic examination (potassium hydroxide (KOH) preparation), histopathology or cultures of the clinical specimen to determine the presence of fungi. Conventional onychomycosis diagnostic methods have several limitations including a high rate of false negatives which result in suboptimal or a lack of treatment regimens, timeframes (results can take days to weeks), and the need for skilled personnel. Polymerase chain reaction assays are notably faster than traditional testing procedures (24 hours rather than days or weeks) and have the ability to identify pathogens that have been resistant to prior care. Molecular methods appear to hold promise in guiding optimal treatment regimens when prior treatments have failed.

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

Identification of Microorganisms Using Nucleic Acid Probes

References

1. American Academy of Dermatology Association. Choosing wisely: Recommendations about treatments, tests, and procedures. 2024; https://www.aad.org/member/clinical-quality/clinical-care/wisely. Accessed August 8, 2024.
2. Caldwell, B., Uchmanowicz, K., Kawalec, J. S., Petrofski, S., & Kurzel, C. (2020). Commercial Multiplex Polymerase Chain Reaction versus Periodic Acid-Schiff Testing for the Diagnosis of Onychomycosis. *J Am Podiatr Med Assoc*, 110(6). https://doi.org/10.7547/18-048.
3. 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.
4. Goldstein, A.O., Bhatia, N. "Onychomycosis: Epidemiology, clinical features, and diagnosis." 2024. *Up-To-Date*. https://www.uptodate.com/contents/onychomycosis-epidemiology-clinical-features-and-diagnosis?search=onychomycosis&source=search_result&selectedTitle=2%7E55&usage_type=default&display_rank=2#H98379461. Accessed August 8, 2024.
5. 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
6. Lubis, N. Z., Muis, K., & Nasution, L. H. (2018). Polymerase Chain Reaction-Restriction Fragment Length Polymorphism as a Confirmatory Test for Onychomycosis. Open Access *Maced J Med Sci*, 6(2), 280-283. https://www.ncbi.nlm.nih.gov/pubmed/29531588.
7. Navarro-Pérez D, García-Oreja S, Tardáguila-García A, et al. "Microbiological culture combined with PCR for the diagnosis of onychomycosis: Descriptive analysis of 121 patients." Mycoses. 2023 Dec;66(12):1045-1049. doi: 10.1111/myc.13648. Epub 2023 Aug 13. PMID: 37574461.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 8/7/24, 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)
1/1/24	10/17/23		Routine maintenance (slp) Vendor managed: Avalon
1/1/25	10/15/24		• Routine maintenance (slp) • Vendor managed: Avalon • Policy stance changed to EST

Next Review Date: 4th Qtr, 2025

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)	Covered, with criteria
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.