Confirmatory Testing for Onychomycosis—Reply

in combination with the present patient's classic cutaneous presentation, would indicate that the full spectrum of NLE's manifestations can occur in the absence of autoimmunity in the maternal genetic donor. Therefore, from a clinical perspective, we suggest that NLE should be considered possible in an infant when there is a history of autoimmune connective tissue disease or appropriate circulating IgG autoantibodies in the gestational mother.

Albert Sean Chiou, MD
Grace Sun, MD
Jinah Kim, MD, PhD
Kevin Chun-Kai Wang, MD, PhD
Ann L. Marqueling, MD

Author Affiliations: Department of Dermatology, Stanford University School of Medicine, Palo Alto, California (Chiou, Kim, Wang, Marqueling); Dermatology Medical Group of Oxnard and Camarillo, Camarillo, California (Sun).

Corresponding Author: Ann L. Marqueling, MD, Department of Dermatology, Stanford University School of Medicine, 770 Welch Rd, Ste 261, Palo Alto, CA 94304 (annlm@stanford.edu).

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COMMENT & RESPONSE

Confirmatory Testing for Onychomycosis

To the Editor We read with great interest the article by Mikailov et al[1] on the cost-effectiveness of laboratory testing before treatment of onychomycosis. In this article, the authors did a substantial analysis of the cost and potential harm associated with 3 methods of onychomycosis assessment prior to therapy with oral terbinafine or efinaconazole, 10%. They include the potassium hydroxide and periodic acid-Schiff stainings, which are commonly performed in dermatological practices. Fungal culturing should be included because it is the only test that can prove the viability and identity of the organism. It is particularly important when nondermatophytes or yeast are suspected, which may not respond to terbinafine.

The authors stress that traditionally, confirmatory testing before treating onychomycosis was largely driven by drug costs. However, there are more compelling reasons to perform this testing that are not based on economics alone. Empirical treatment of nail dystrophy that is assumed to be onychomycosis may result in treatment failures and incorrect diagnoses. While onychomycosis is the most common nail disorder, it may present similarly to benign nail diseases, including lichen planus, psoriasis, verruca, bacterial infections, subungual exostosis, and onychomatricoma,[2] each requiring vastly different treatments. An erroneous diagnosis would be even more detrimental with malignant nail conditions, such as squamous cell carcinoma and melanoma.[2] Furthermore, while highly trained dermatologists and podiatrists may be able to make the diagnosis of onychomycosis clinically in many cases, general practitioners and physician extenders would have less diagnostic precision. All things considered, treatment for presumed onychomycosis without laboratory confirmation may cause misdiagnosis, serious complications,[3] and medicolegal costs.

Mikailov et al[1] properly base their cost calculation on the incidence of clinically apparent liver injury due to terbinafine. However, additional clinically significant adverse effects of terbinafine, including severe neutropenia and toxic epidermal necrolysis,[4] should also be included. To be complete, the other oral treatment option approved by the US Food and Drug Administration, itraconazole, with potential adverse effects such as liver failure, peripheral neuropathy and cardiovascular events,[5] should be analyzed. Both of these oral medications may also interact with the patients' existing drugs through the CYP450 system, causing other adverse effects.

While Mikailov et al[1] have written an important cost analysis on laboratory confirmation prior to treatment for onychomycosis, as dermatologists we have an obligation to weigh other factors, such as patient morbidity and mortality. We strongly advocate that physicians confirm the diagnosis before initiating treatment in all cases of nail dystrophy.[3]

Shari R. Lipner, MD, PhD
Richard K. Scher, MD

Author Affiliations: Department of Dermatology, Weill Cornell Medicine, New York, New York.

Corresponding Author: Shari R. Lipner, MD, PhD, Department of Dermatology, Weill Cornell Medicine, 1305 York Ave, New York, NY 10021 (shl9032@med.cornell.edu).

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To the Editor Mikailov and colleagues[1] propose that the empirical treatment of onychomycosis with terbinafine without confirmatory testing is cost-effective. While the approach may be reasonable when disease prevalence is exceedingly high, prescribing medications with known adverse effects, some serious, leads to delay in correct treatment and unnecessary therapy for patients with dystrophic nails who do not have onychomycosis. In fact, only about half of dystrophic nails are caused by fungi[2,3]; the other half are manifestations of psoriasis, lichen planus, and trauma, among other causes. If empirical treatment is provided for clinically suspected onychomycosis in dystrophic nails, correct treatment is delivered only half the time, the same probability as a random coin flip. The calculations of cost savings using 75% disease prevalence by Mikailov et al[1] overestimate savings. Fingernail dystrophy without toenail involvement is seldom caused by a dermatophyte; therefore, empirical treatment with terbinafine should be administered with caution. Furthermore, recent meta-analyses for the prevalence of onychomycosis in Europe and North America estimate it to be only 4%, with previous reports of 7% to 14% in North America.[3-5]

Mikailov et al[1] also discuss the cost savings for liver function test monitoring during terbinafine therapy. While the incidence of apparent liver injury from terbinafine is low, one needs to consider quality of life issues and financial repercussions of other adverse effects such as dysgeusia, gastrointestinal upset, and more serious systemic manifestations including DRESS syndrome (drug reaction with eosinophilia and systemic symptoms), Stevens-Johnson syndrome, and toxic epidermal necrolysis. These rare but serious complications should not be taken lightly, especially when terbinafine is prescribed for patients who do not need the medication to begin with.

The beauty of medicine lies in the ability to arrive at the proper diagnosis using astute clinical judgment and appropriate ancillary testing. What happens to the art of medicine when the physician no longer provides expertise in diagnosis but, instead, prescribes low-cost medications as "a shot in the dark," hoping, on the basis of a only a high disease-prevalence rate, that most patients will be covered? Will future suggestions be to empirically treat "rashes" with a cocktail of oral steroids and antifungal agents to save on specialist visits and biopsy costs? Or will these "low-risk" medications be offered over the counter, without the need for physician supervision or laboratory monitoring? Perhaps it is time to rethink cost savings at the expense of thoroughness in diagnosis and to provide appropriate treatment with high-quality care for our patients.

Apphia L. Wang, MD
Boni E. Elewski, MD
Craig A. Elmets, MD

Author Affiliations: Department of Dermatology, University of Alabama at Birmingham School of Medicine, Birmingham.

Corresponding Author: Apphia L. Wang, MD, Department of Dermatology, University of Alabama at Birmingham School of Medicine, 1720 Second Ave S, Eye Foundation Hospital, Ste 414, Birmingham, AL (Apphia@gmail.com).

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In Reply We thank Wang et al and Lipner and Scher for their interest in our study and agree with both groups about other potential consequences of terbinafine use.[1] Our analysis of the adverse effects of terbinafine included only hepatic manifestations, given the US Food and Drug Administration and package insert recommendations to check transaminases prior to initiation of therapy and the availability of reliable incidence statistics from the National Library of Medicine LiverTox database. The other adverse effects mentioned by Wang et al and Lipner and Scher are certainly important; incidence statistics are not available for those adverse events, however, limiting our ability to perform a similar analysis. Nevertheless, we emphasize shared decision making with patients before prescribing systemic medications with the potential for idiosyncratic adverse drug reactions.

We likewise agree with Lipner and Scher that a fungal culture is the best test to identify organisms. However, potassium hydroxide and periodic acid–Schiff are the most widely used and appropriate tests to consider in the initial workup, as fungal cultures have such poor sensitivity, poor negative predictive value, and delayed time to diagnosis.[2,3] Of course, if a nondermatophyte is suspected, such as in refractory disease, a culture should be taken. Although primary care physicians are less accurate than dermatologists in their clinical diagnosis of onychomycosis, our data suggest that empirical treatment is still favored at their level of accuracy.[4]

While Lipner and Scher correctly point out that itraconazole therapy is also approved for onychomycosis, we chose to model a more common treatment for simplicity. Future studies could include other treatment options such as weekly fluconazole pulsing, which is cheap, effective, and obviates much of the monitoring tests and interaction risks of terbinafine and itraconazole.[5]

We would like to directly address the major concerns of Wang et al, which arise from a misinterpretation of our methods and a different standard for how one defines the "art" of medicine. To clarify, our study focuses on the cost-effectiveness of confirmatory testing, not diagnostic testing. Patients in whom the diagnosis is unclear should be tested. However, if a dermatologist's clinical diagnosis is onychomycosis, he or she is correct between 65% and 95% of the time.[2,3,6] The quoted baseline 4% prevalence of onychomycosis in society is irrelevant because our study focuses on the prevalence among patients who have

been given clinical diagnoses by dermatologists. Likewise, the cited article by Gupta et al[7] is based on a different patient population; those findings should not be extended to the management of patients who present with onychodystrophy and have clinical findings of onychomycosis.

We would also like to stress that we do not propose any cost savings from reduction of liver function monitoring; our models account for standard monitoring of terbinafine regardless of confirmatory testing. Similarly, we did not evaluate or comment on fingernail dystrophy, and our analysis should not be extended to those patients.

The beauty and art of medicine is embodied by the astute clinician who integrates up-to-date evidence, clinical diagnostics, and patient values to determine the most appropriate management strategy; the antithesis is a 1-size-fits-all approach that requires indiscriminate wholesale testing. Assuming that a dermatologist's clinical diagnosis of a common disease such as onychomycosis is a "shot in the dark" demeans our specialty and restricts us to being overpaid manicurists, blindly clipping nails without a second thought.

While no physician wants to miss a diagnosis or give a medication that causes an adverse effect, we must consider the cost associated with our own inability to tolerate risk. The gold standard for the diagnosis of melanoma is histologic analysis: should we biopsy every nevus?

A belt-and-suspenders approach is not art but rather a reflection of a culture that defers to testing over thinking—even if it results in unnecessary costs that are often passed on to patients and the health system at large. Our findings seek to repudiate this culture and enable the true art of thoughtful medical practice that values physicians' clinical training and diagnostic accuracy.

We hope that our study empowers dermatologists by removing arbitrary guideline mandates and allowing evidence-based medicine to combine with clinical insight to guide a management strategy in line with patient goals.

Anar Mikailov, MD
Cara Joyce, PhD
Arash Mostaghimi, MD, MPA, MPH

Author Affiliations: Department of Dermatology, Brigham and Women's Hospital, Boston, Massachusetts (Mikailov, Mostaghimi); Walgreen Co, Deerfield, Illinois (Joyce).

Corresponding Author: Arash Mostaghimi, MD, MPA, MPH, Department of Dermatology, Brigham and Women's Hospital, 75 Francis St, PBB-B 421, Boston, MA 02115 (amostaghimi@partners.org).

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