

Toenail Assessment Tool for Quantitation of Visibly Infected Mycotic Nail Plate in Onychomycosis

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Typically, the amount of mycotic nail involvement in onychomycosis (fungal infection of the nail) before and after drug therapy is determined visually. Because there is an inherent element of subjectivity, it is difficult to accurately measure and compare results across clinical trials or to assess how much improvement has been achieved in response to therapy. We developed a simple tool for measuring mycotic nail involvement. This novel tool consists of a large grid containing 5 toenail templates of varying nail morphologies that are derived from the actual shape of the toenail of the great toe in several males and females, and one standardized computer-generated nail shape. The toenail templates are presented in 7 different sizes to match different nail sizes. Each toenail template is further divided into 8 segments, each comprising approximately 12.5% of the total nail surface. Measurement of the percentage of

mycotic nail involvement is accomplished by the following procedure: (1) placing tracing film over the target toenail; (2) tracing the outline of the entire toenail, followed by tracing the affected portion of the toenail on the same film; (3) placing the tracing film over a nail template on the grid that best fits the shape of the toenail; and (4) counting the number of grid segments that correspond to 50% or more involvement. To assess feasibility, the tool was used in a large randomized trial involving over 30 sites and 500 subjects with onychomycosis. This tool is a more accurate and less biased alternative to visual assessment for measuring nail involvement or progression of nail clearing.

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Onychomycosis is defined as a mycotic infection of the keratinized tissue of the nail plate and nail bed.¹ The typical diagnosis is by a combination of clinical observation, fungal cultures, and/or direct microscopy with potassium hydroxide (KOH).² Occasionally, other methods such as periodic acid-Schiff or fluorescent staining techniques are used for enhanced sensitivity. The clinical features include subungual debris (severe thickened hyperkeratosis), discoloration, longitudinal darkened striations, thickening of the nail plate, onycholysis (detachment of the nail from the nail bed), and brittle damaged nail.³ Both topical and oral antifungal agents are used to effectively treat nail infections, with varying success.⁴ The objective of successful treatment is to achieve clearing of the affected nail(s), the so-called clinical cure, which occurs when the new nail plate

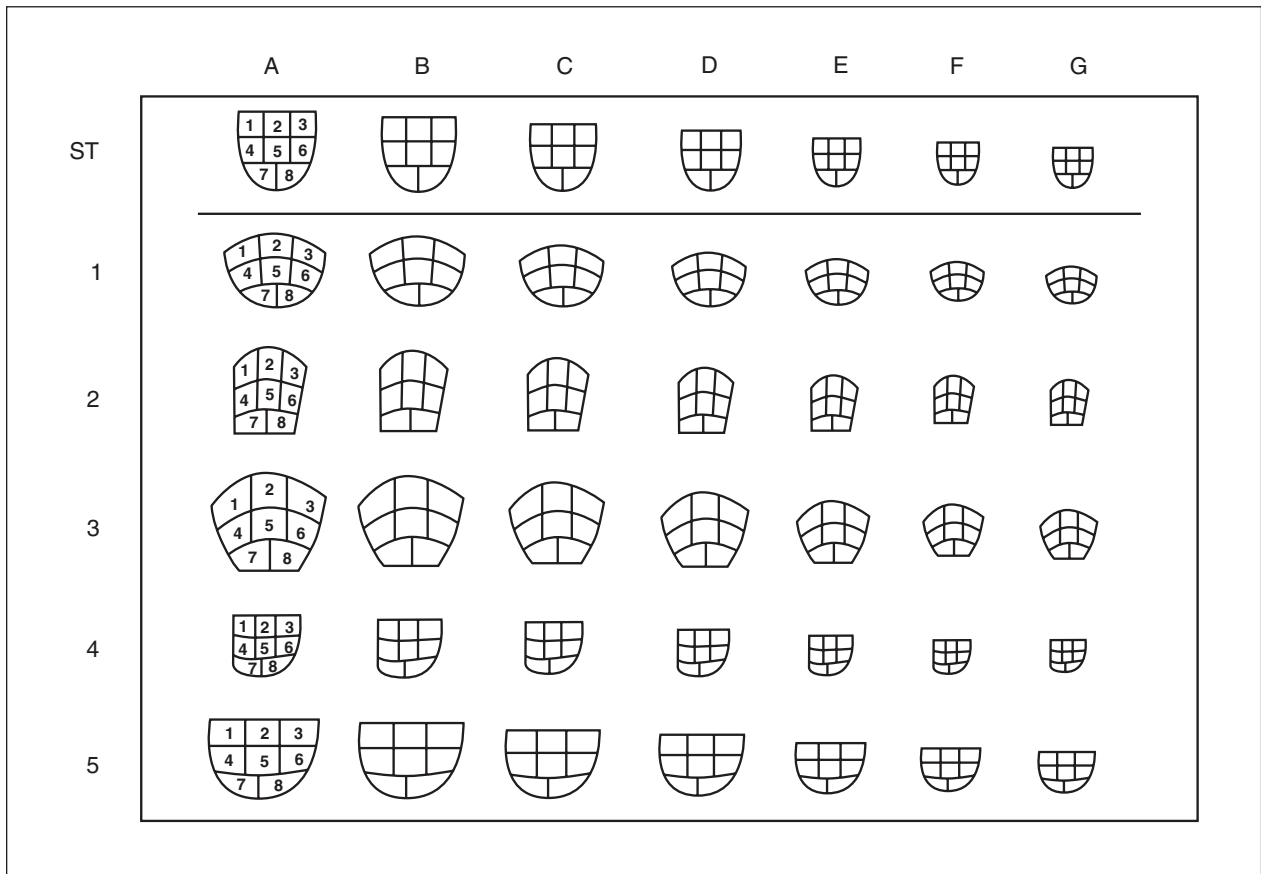


Figure 1. Toenail templates of different shapes (1–5) and sizes (A–G) contained in the toenail grid. Templates of the toenail of the great toe (right and left) are based on 5 actual nail shapes and 1 standardized (ST) nail shape.

is either completely or almost completely devoid of visible fungal infection.³ The key to assessing clinical cure is the ability to accurately measure the percentage of mycotic involvement of the nail relative to total nail plate surface, both before and after commencing treatment. Both physician and patient expectation of the end result of therapy is to obtain almost completely clear nails. However, effective treatment may require months of therapy, and the slow rate of nail growth means that nail appearance changes gradually,⁵ making it imperative to have an objective method of assessing and documenting clearance.

The foundation of good clinical practice is based on the ability to interpret the results of clinical trials. Generally, the assessment of visibly infected nail area or nail clearing is approximated by the investigator's visual estimation, which is subjective, nonstandardized, and potentially inaccurate because of investigator variability and bias.⁶ A review of the literature illustrates the variability that exists. For example, in a clinical trial conducted by Meyerson et al⁷ in 1992, the investigators measured by visual approximation the distance between the cuticle and

the most proximal onychomycotic nail border. The investigators recorded the percentage of involvement in 25% increments, again by visual approximation.⁷ In 1999, Glyn et al⁸ measured clinical effectiveness as mycologic cure and at least 5 mm of new clear growth. The same year, Wadhams et al⁹ used a 3-part score: area involved plus pain plus thickness. A score of zero was considered a clinically healthy nail.⁹ In a clinical trial conducted by Lecha¹⁰ in 2001, a 3-point scale defined cure as 95% clearance by visual assessment. The author defined *improved* as 20% clearance, while *failed* included little to no clearing, again by visual assessment.¹⁰

In 2000, Baran et al¹¹ used a scoring assessment in a clinical trial that evaluated terbinafine hydrochloride monotherapy versus amorolfine lacquer 5%. The authors' scoring system visually delineated the nail into 9 sections; each section was approximately 11% of the total nail.¹¹ Although this system was an improvement over the other scoring systems, the assessment still was conducted via visual interpretation. The variation would become a bigger problem if nail assessments were done as part of measuring therapeutic response in multicenter clinical trials

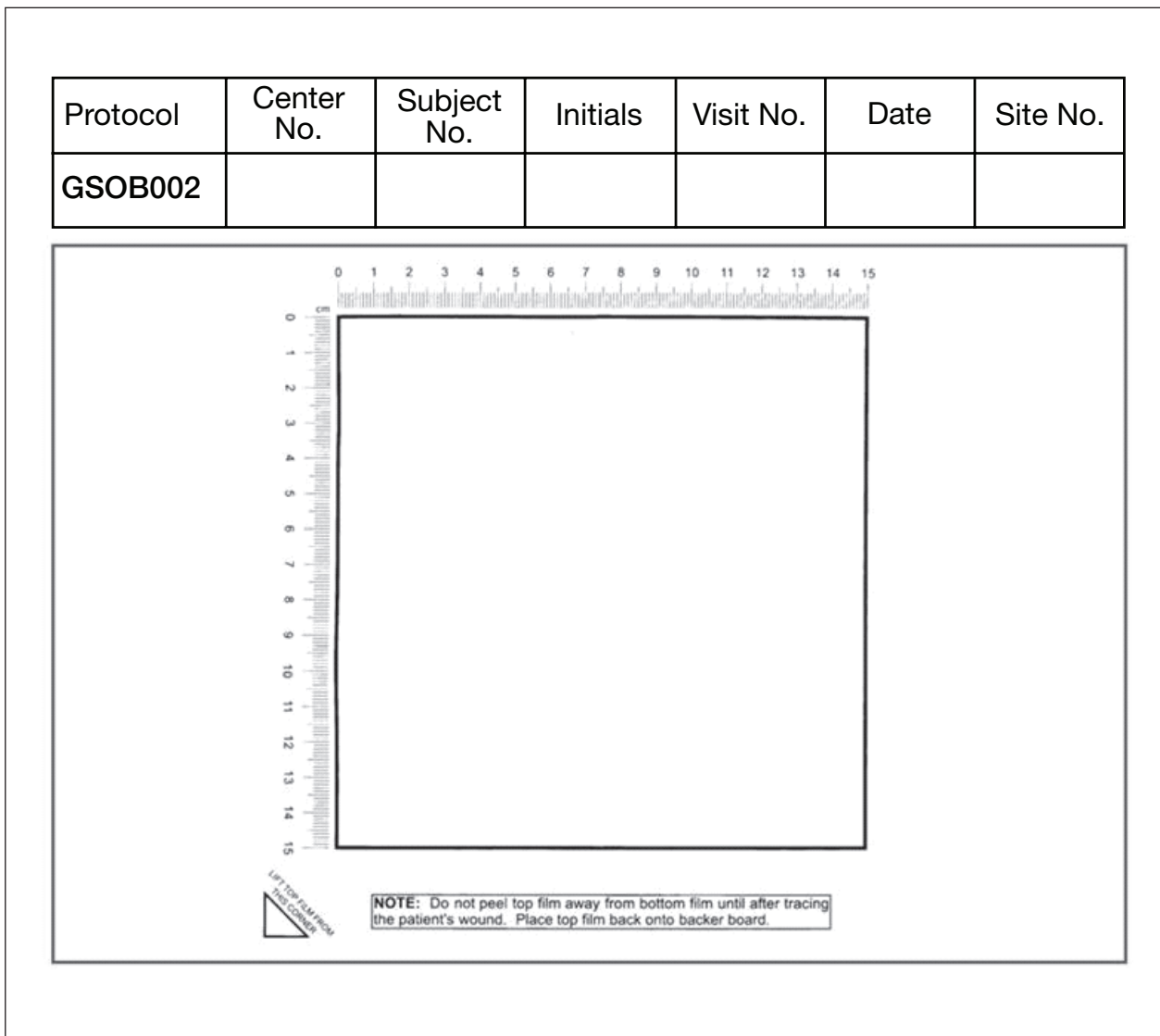


Figure 2. Static cling film used for tracing toenails.

with investigators of varying experience and skills. Naturally, such variation can impact drug efficacy results either positively or negatively. Because clinicians typically base their judgment of drug efficacy and choice of therapy on results presented in the drug manufacturers' prescribing information or on results of subsequent trials performed either through sponsored research or by independent investigators, an easy-to-use method to allow standardization of efficacy assessment may be appreciated.

Prior studies evaluated an easy-to-use inexpensive assessment tool for more accurate objective measurements of visibly infected toenails as well as for monitoring the progress of nail clearing.¹²⁻¹⁵ We now describe this tool in detail and report the feasibility of using this tool for formal assessment of therapeutic response of toenail onychomycosis.

Assessing Nail Improvement

In preparation for a large, multicenter, clinical trial using investigators with little or no experience, a mycotic nail involvement assessment tool was developed.^{12,13} The purpose of the tool was to assist investigators with their assessment of nail involvement and drug efficacy. The study population consisted of 504 outpatients aged 18 to 75 years. Subjects were randomized into 2 nearly equal treatment groups (terbinafine hydrochloride, terbinafine hydrochloride plus debridement). All subjects included in the study had confirmed clinical diagnosis of toenail onychomycosis as determined by positive mycologic culture and positive KOH test results. Subjects had at least one target toenail (toenail of great toe) affected by moderate to severe dermatophyte infection and were able to provide written consent.¹³

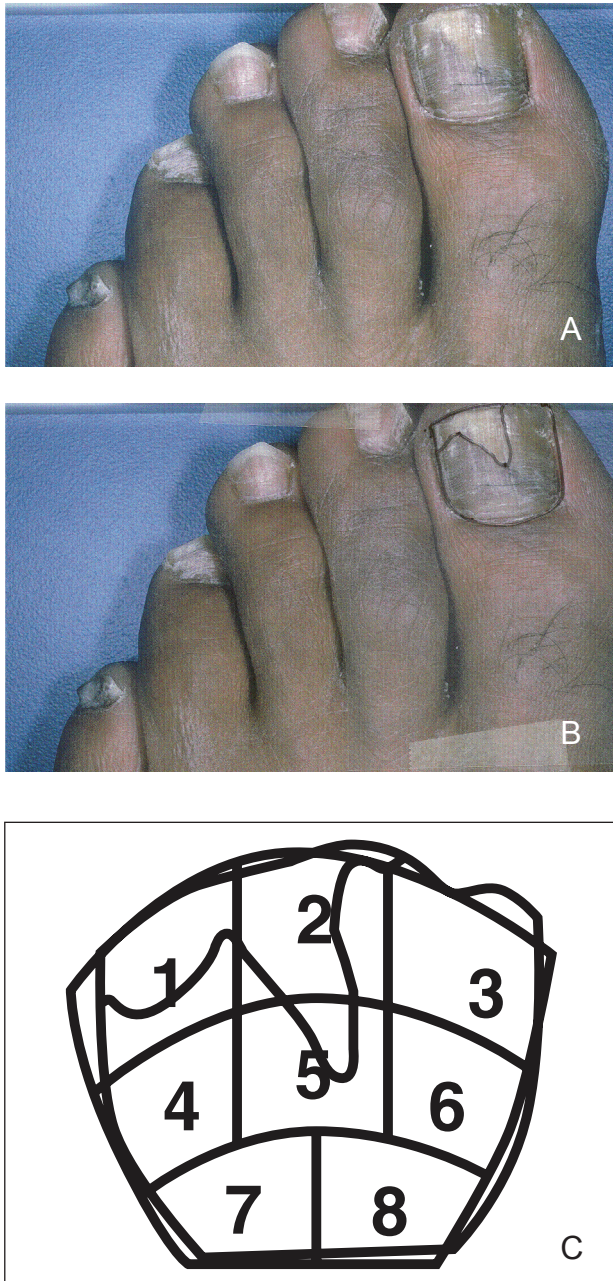


Figure 3. A mycotic toenail (great toe)(A) and tracing of the toenail and affected area (B). More than 50% of segments 1 and 2 are affected (C). Therefore, the total toenail area affected is 25% ($\geq 50\%$ of an affected segment corresponds to 12.5% toenail involvement). In segment 3, less than 50% is affected, so it is not counted.

The toenail of the great toe was used for evaluation of clinical cure. The details of this study have been described elsewhere.^{13,14}

Clinical Efficacy Assessment—The primary analysis time point was week 48, which was designated as the principal time point for clinical cure assessment. However, the extent of nail involvement was

measured at baseline and again at each visit throughout the study. To confirm that clinical cure was accompanied by eradication of the fungus, cultures and KOH tests also were performed by an independent central laboratory.¹⁵

Toenail Grid—The tool used in the trial consisted of a series of templates of the toenail of the great toe based on 5 actual nail shapes and 1 standardized nail shape (Figure 1). Seven different sizes of each nail shape are provided in the tool to allow for more accurate measurement of toenails of various sizes. The templates are positioned on a laminated double sided sheet of paper 0.2-mm thick. One full set of toenail templates of varying shapes and sizes is on one side of the grid, while a set of mirror images is on the other side, providing an easy and convenient method of measurement of the toenail of the great toe (right and left). Each template is divided into 8 nearly equal segments (each approximately one eighth [12.5%] of the total nail surface). The 2 segments closest to the proximal nail fold are smaller to better represent nail plate anatomy.

Toenail Tracing Film—A clear, two-ply, vinyl, static cling film is placed over the target nail and is used to obtain an outline of the nail (Figure 2). The static cling film is loosely adhered to a laminated backer board and features a square box that is bordered by 2 centimeter rulers. There are spaces along the upper part of the square box for entering patient identification, site identification, and study number for accurate tracking. The rulers can be used for measurement of the affected toenail. After the film is positioned on the nail, the outline of the involved nail plate is traced using a 0.5-mm fine point pen.

Experimental Procedure—The static cling film is first labelled with each subject's number, initials, visit number, and date of visit. The film is then peeled away from the backer board and placed over the target toenail. An outline of the entire toenail is obtained first. Then, the affected area of the toenail is delineated on the same film. Next, the tracing film is placed over a nail template on the grid that best fits the shape of the toenail. Finally, each segment with a surface that is occupied by 50% or more of the visibly affected toenail is counted as corresponding to 12.5% toenail involvement (Figure 3). All segments are counted and the percentage of toenail involvement is tabulated. The film can be used as a permanent record.

Reported Use of Toenail Assessment Tool

The toenail grid and templates developed together with tracing paper and reported here were used to generate the data published in 2 previous reports.^{12,13} The determination of a subject's disease severity often is required in clinical trials prior to subject

Subjects and Percentage of Nail Area Affected for Each Treatment Group at Baseline as Measured by the Toenail Assessment Tool

Nail Area Affected, %	Treatment Group		Total, n (%) (N=489)
	Terbinafine Hydrochloride, n (%) (n=243)	Terbinafine Hydrochloride + Debridement, n (%) (n=246)	
0–25	11 (4.5)	7 (2.8)	18 (3.7)
26–50	44 (18.1)	47 (19.1)	91 (18.6)
51–75	83 (34.2)	95 (38.6)	178 (36.4)
76–100	105 (43.2)	97 (39.4)	202 (41.3)

randomization. In previous reports, the investigators measured the extent of nail involvement from each subject’s target toenail at baseline and at each subsequent visit.^{12,13} The visits were spread over 48 weeks and conducted at weeks 6, 12, 24, and 48. The extent of mycotic nail involvement was determined based on a target toenail measurement. The results showed that subjects fit into 4 groups based on the extent of nail involvement, as shown in the Table, which also shows the percentage of subjects in each treatment group.

The investigators then used the toenail grid to measure change from baseline over 48 weeks in response to terbinafine hydrochloride (n=243) or terbinafine hydrochloride plus debridement (n=246).¹³⁻¹⁵ Improvements in nail appearance could be seen and measured as early as week 6. The clear nail growth was measured throughout the study and increased in almost a linear fashion until week 48 (Figure 4). The toenail grid also was used to determine the proportion of subjects who responded to therapy in each treatment group.¹³ The percentage of subjects with clinical cure (defined as ≥87.5% clearing of the toenail of the great toe) at weeks 6, 12, 24, and 48 for the terbinafine hydrochloride monotherapy versus the terbinafine hydrochloride plus debridement treatment groups

were 2.9% versus 3.7%; 7.4% versus 11.8%; 23.5% versus 35.0%; and 51.4% versus 59.8%, respectively. A larger percentage of subjects showed clinical cure in the terbinafine hydrochloride plus debridement treatment group than in the terbinafine hydrochloride monotherapy treatment group. The toenail assessment tool clearly discriminated between the 2 treatment modalities.¹³

Comment

Traditionally, the mycotic involvement of the nail is assessed by visual estimation. The objective of developing this toenail assessment tool was to

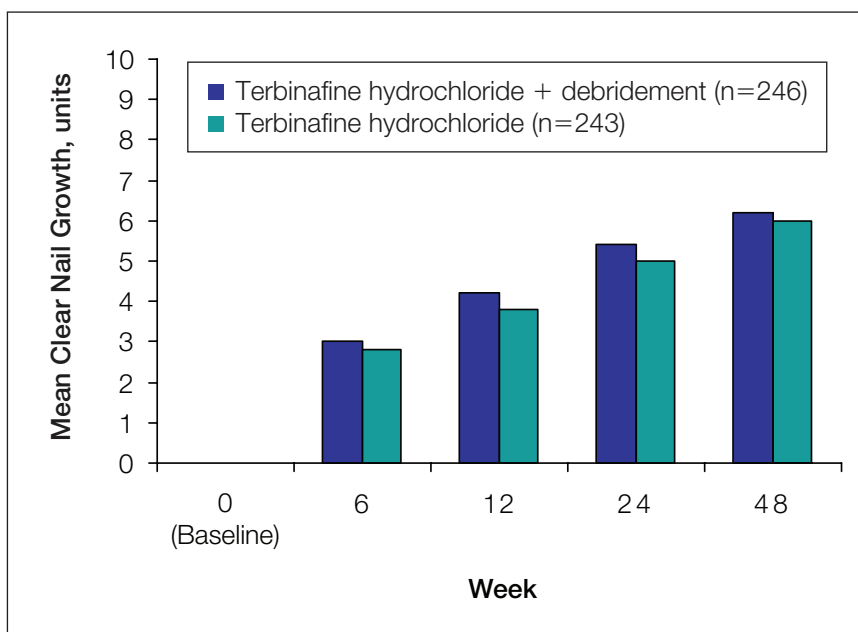


Figure 4. Mean clear nail growth (1 unit=12.5% toenail involvement) as determined by the toenail assessment tool.

create a more standardized and simple method for the accurate assessment of either mycotic involvement and/or toenail clearing, and to minimize investigator subjectivity. The new tool allowed for more accurate measurement of therapeutic response and temporal regression of mycotic nail during the 48-week study. Each segment with a surface that was occupied by 50% or more of the visually affected toenail was considered to have mycotic involvement in that segment (12.5% toenail involvement). Thus, by definition, the segments with less than 50% mycotic involvement were considered to have 0% toenail involvement, even though in reality these segments could have had mycotic involvement ranging from greater than 0% to 6.25% or less. In our opinion, this may not be an issue because all toenails will be evaluated similarly, changes are relative, and the gain from consistency outweighs this small disadvantage.

Toenails are 2-dimensional objects that often are concave, whereas the assessment tool is only 1-dimensional. Hence, the tool does not account for the concave surface of the toenail. When placing the traced toenail on the toenail grid, it is possible that the tracing will not completely match the template, which may distort the grid and the resulting measurement. However, this did not appear to affect the tool's ability to measure nail involvement. The flexibility of the tracing film is forgiving and allowed good tracings of the toenail to be obtained; this sentiment was shared by many of the investigators.

Although attempts have been made to develop new nail assessment tools and methodologies, such as computerized planimetry, these techniques are complex, expensive, and require a major investment in photographic equipment. Recent studies have failed to support or recommend planimetry to measure toenail mycotic involvement. In one study, after using planimetry to quantify clinical cure, the author recommended using a measurement template consisting of a clear acetate sheet printed with rectangles of known dimension.¹⁶ The author placed the clear sheet over the toenail to select a rectangle that corresponded to the entire surface area of the toenail and the area of infection. However, too few subjects had template measures performed.¹⁶ More recently, planimetry was used to determine therapeutic response to 2 different formulations of oral antifungal agents in a large, double-blind, placebo-controlled, multicenter trial of approximately 2000 subjects with onychomycosis. The authors later criticized the planimetry as having shortcomings.¹⁷

Although the toenail assessment tool discussed here provides an easy-to-use and inexpensive method to allow greater consistency across clinical trials, it is not perfect. Because not all toenail shapes and sizes

are represented on the tool, the investigator must choose the closest matching toenail template, which was not a problem in studies of more than 500 subjects.¹³⁻¹⁵ Furthermore, the clinical cure as measured by the toenail assessment tool correlated well with improvements in the subjects' quality of life, which suggests the tool accurately reflected changes measured in the toenail.^{18,19} Moreover, an informal poll indicated that most investigators were able to find at least one template that matched a given toenail, suggesting that there was not a great variation in the target toenail sizes. However, one way to improve the assessment tool is to develop a static cling film of templates that could be directly applied to the nail to avoid the need to read off a rigid template.

Conclusion

The toenail assessment tool presented here provides an easy method for measuring mycotic nail involvement and therapeutic response in a clinical setting, particularly during clinical trials, or as documentation to show the patients' improvements in their nail following therapy. The tool can be reproduced by almost anyone, and the necessary tracing film and writing pens are available at nominal costs. Additionally, the record keeping is easy, and the results indicate that high-quality data can be generated.

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