

Early Clinical results: New combination

Topical Antifungal and Cosmetic solution
for Treatment of Toenail Dystrophy

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ANTIFUNGAL/NAIL RENEWAL SOLUTION

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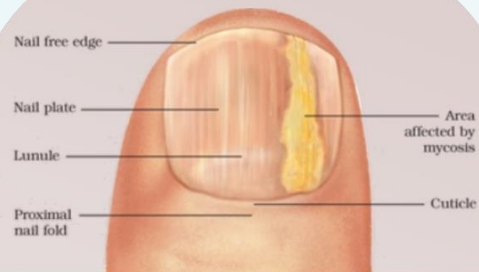
Disclosures

This study reports the results of clinical improvement for both Fungal and Non-fungal toenails. It also reports the cure rate for Onychomycosis which is considered an off-label use.

Consultant for
Marlinz Pharma

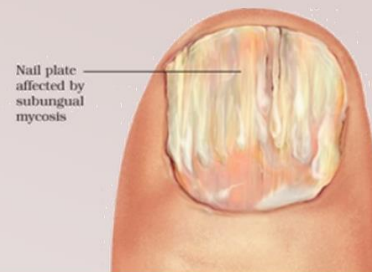
Onychomycosis:

Clinical presentation



**Distal and Lateral
Subungual**

Nail plate
affected by
subungual
mycosis



Candida

White nail
plate resulting
from mycosis



**Superficial
White**

Proximal
nail plate affected
by subungual
mycosis



**Proximal
subungual**

Complete
nail
destruction



Total Dystrophic:
Potential endpoint of all forms
– entire nail plate and nail bed
involvement.

Most common nail disease of Adults in North America:

Up to 14% of population or 100 million

Psychosocial effects of Toenail Disease

Study

258 Patients perception of
Onychomycosis and QOL

Results

76% Nail-trimming problems

74% Embarrassment

48% Pain

40% Nail Pressure

38% Pain wearing shoes

58 onychomycosis-
related sick days and
468 medical visits
(1.8 per subject)
were reported
during a 6-month
period.

Psychosocial effects of Toenail Disease

Conclusion

Onychomycosis has significant social, psychologic, health, and occupational effects. Relevance of quality-of-life issues to overall health, earning potential, and social functioning should prompt reconsideration of the value of aggressive treatment of onychomycosis.

Toenail Anatomy

Nail plate (0.25–1 mm),

Hard, slightly elastic, translucent,
convex-shaped structure

45-90 layers of dead, keratinized,
flattened cells

Tightly bound cells via numerous
intercellular links, membrane-
coating granules

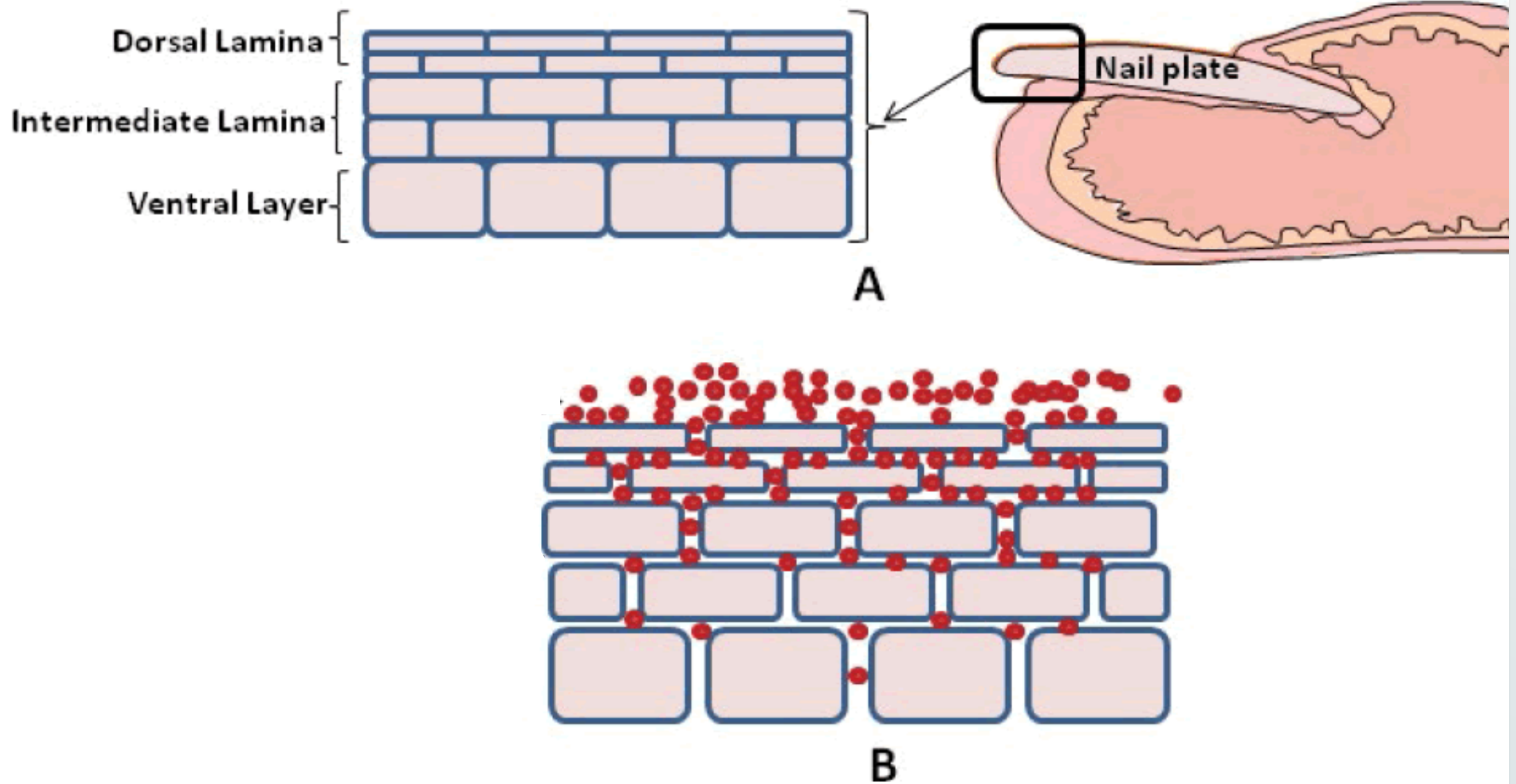


Nail Properties

Properties of toenail:

- › Many experiments – Nail behaves like a hydrophilic gel membrane as opposed to a lipophilic membrane such as stratum corneum.
- › Architecture and composition: Severely limits penetration of drugs

Possible Transport Mechanism through Toenail



Toenail growth

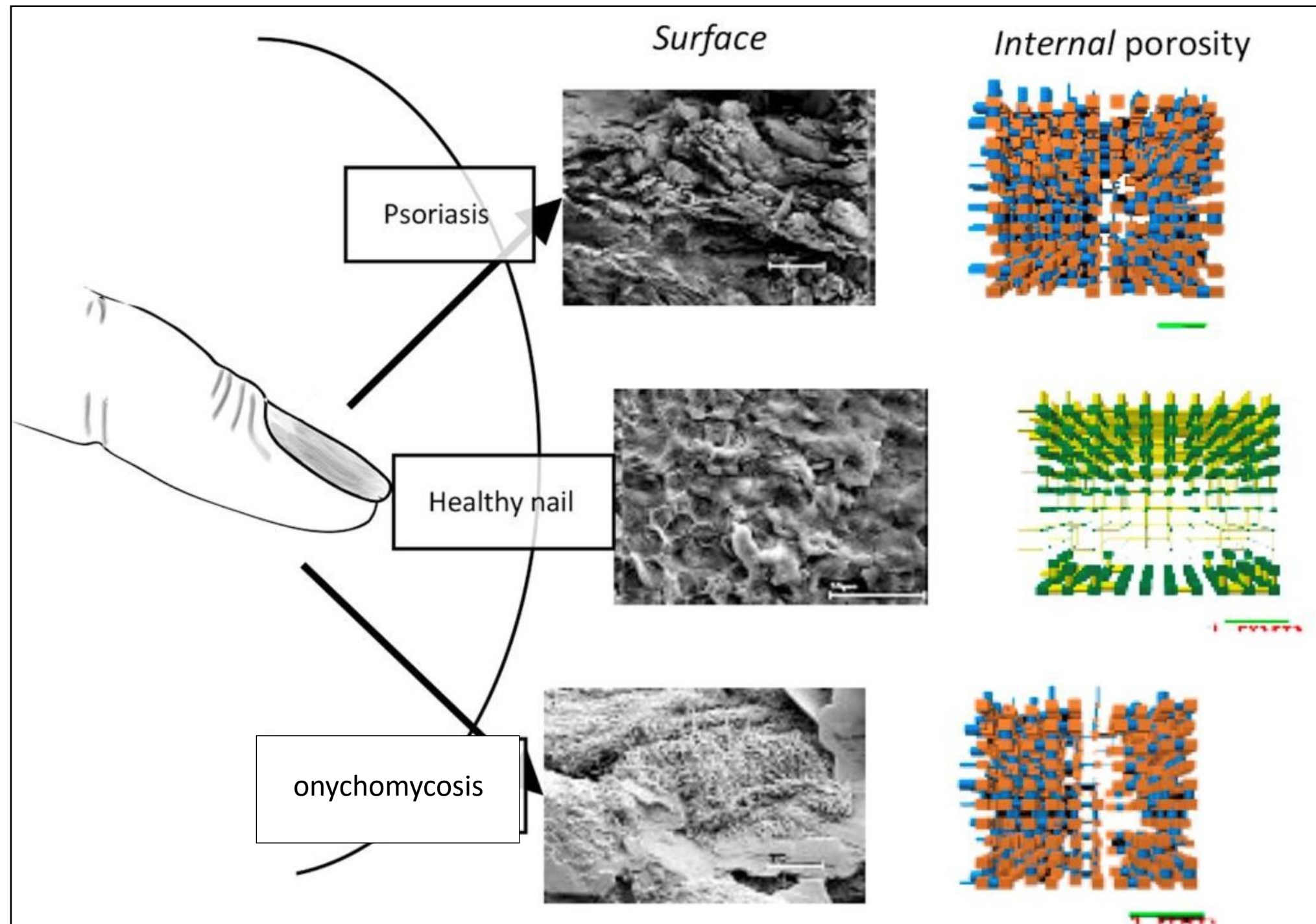
Generally 0.5-1 mm/mo.
in dystrophic toenails

Normally 2-3 mm/mo
in normal toenails

Factors that affect toenail growth:

- › Age (increased) decreases growth
- › Gender: Female > male
- › Climate: Increased temp > lower temp
- › Pregnancy: Increases

Changes in Nail Microstructure



Onychomycosis

Defined:

Fungal infection of the toenails or fingernails that may involve any component of the nail unit, including the matrix, bed, or plate.

Most common etiology: *T. Rubrum*





Meta-analysis of the utility of culture, biopsy, and direct KOH examination for the diagnosis of onychomycosis

Verónica Velasquez-Agudelo^{1,2} and Jaiberth Antonio Cardona-Arias^{3,4*}

Abstract

Background: Onychomycosis is a highly prevalent disease worldwide. There is no standard test for its diagnosis, which remains costly, wasteful, and is sometimes delayed. The diagnostic tests for this disease are few and discordant. The objective was to evaluate the diagnostic validity, performance, and accuracy of culture, nail clipping with Periodic Acid-Schiff –PAS– staining (biopsy), and direct potassium hydroxide (KOH) examination for the study of onychomycosis.

Methods: A systematic review was conducted via meta-analysis using 5 databases and 21 search strategies. An *ex ante* protocol was applied with inclusion and exclusion criteria. Quality was assessed with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool, and the sensitivity, specificity, predictive values, likelihood ratios, diagnostic odds ratios, receiver operating characteristic (ROC) curves, and proportion of correctly diagnosed patients were evaluated with the meta-analysis of studies of evaluations of diagnostic and screening tests (Meta-DiSc) and Epidat using a random effects model.

Results: The efficiency or accuracy of the three tests is influenced by the methodological quality of the studies. These values are lower for KOH and culture and higher for biopsy in moderate quality studies.

Conclusion: The diagnostic tests evaluated in this meta-analysis independently showed acceptable validity, performance, and efficiency, with nail clipping with PAS staining outperforming the other two tests.

Keywords: Onychomycosis, Diagnosis, Validation studies, Test validity, Meta-analysis as topic

Background

Onychomycosis is a highly prevalent infection worldwide with a range between 2% and 30%, corresponding to 50% of nail diseases and 30% of superficial mycoses [1, 2]. Onychomycosis is a cosmopolitan disease, and its incidence increases according to age, climate, physical activity, occupation, and underlying diseases [3]. A higher prevalence has been reported in men, individuals over 60 years of age, patients with immunosuppressive diseases, such as human immunodeficiency virus (HIV) infection or immunological defects, diabetics, and patients with peripheral vascular disease [1]. Its incidence is also higher

in humid and tropical climates, under poverty and overcrowding conditions, and in athletes or sportspersons in whom a higher incidence of tinea pedis has been reported [3, 4].

This disease occurs via fungal invasion of the nail. Over the development course of the infection, there is initial colonisation with subsequent invasion of the nail bed and plate that cause changes in the nail colour, texture, and shape. There are different clinical presentations, including distal subungual, proximal subungual, white superficial, and total onychodystrophy. The distal subungual form is the most common [3, 5].

In addition to the change in nail shape, onychomycosis is related to low self-esteem because those with the condition often experience shame at being associated with poor hygiene and as a source of transmission to other individuals in their surroundings. Onycl

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KOH, Culture and PAS Testing

Sensitivity Values:

Culture:
23% - 84.6%

KOH:
44% - 100%

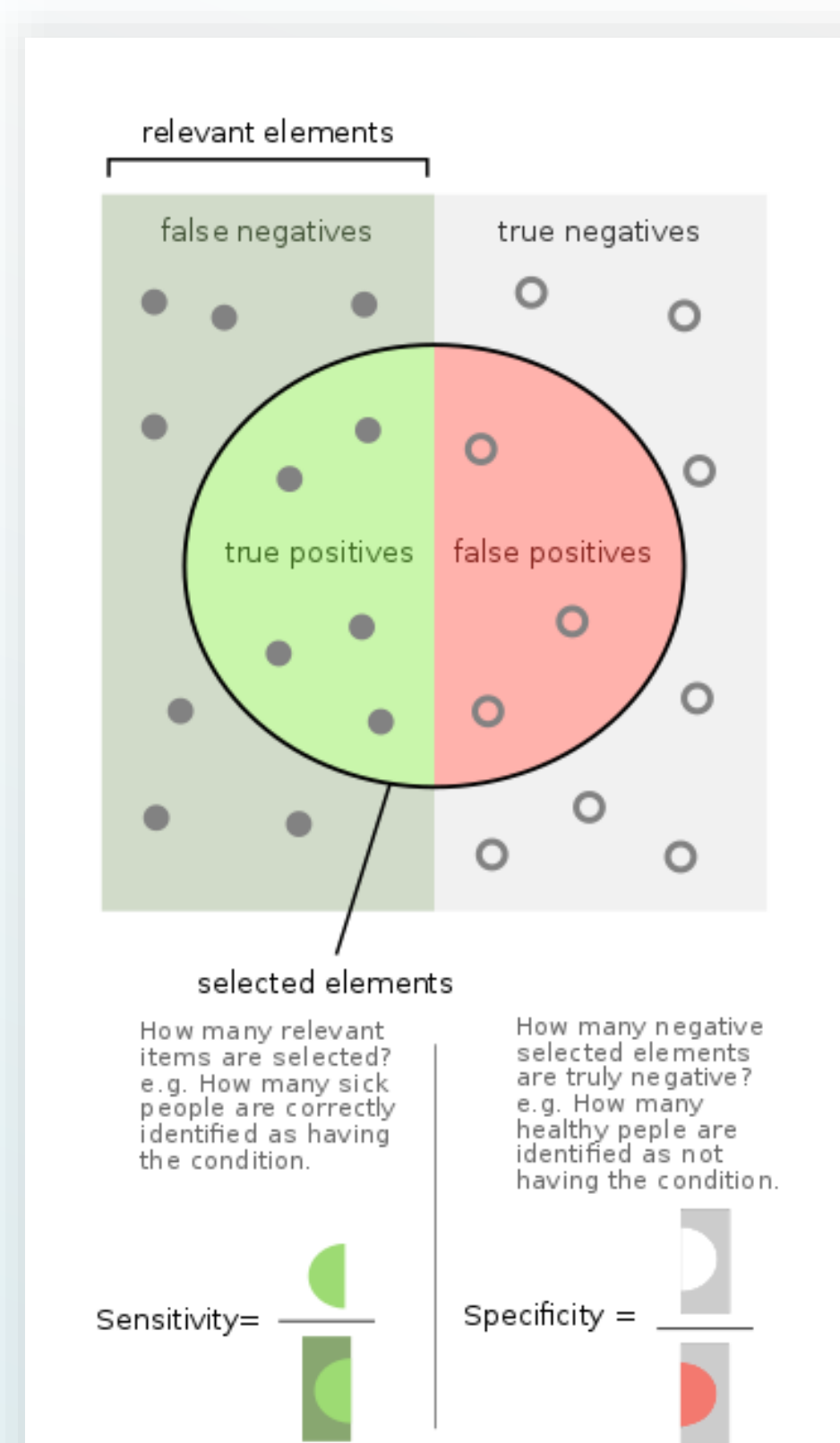
PAS/biopsy:
81% - 91.6%

Test combinations:

PAS/Biopsy & KOH
57%

PAS/Biopsy & Culture
98.3%

- › **Sensitivity** (also called the **true positive rate**, the recall, or **probability of detection** in some fields) measures the proportion of actual positives that are correctly identified as such (e.g., the percentage of sick people who are correctly identified as having the condition).
- › **Specificity** (also called the **true negative rate**) measures the proportion of actual negatives that are correctly identified as such (e.g., the percentage of healthy people who are correctly identified as not having the condition).



KOH, Culture and PAS Testing

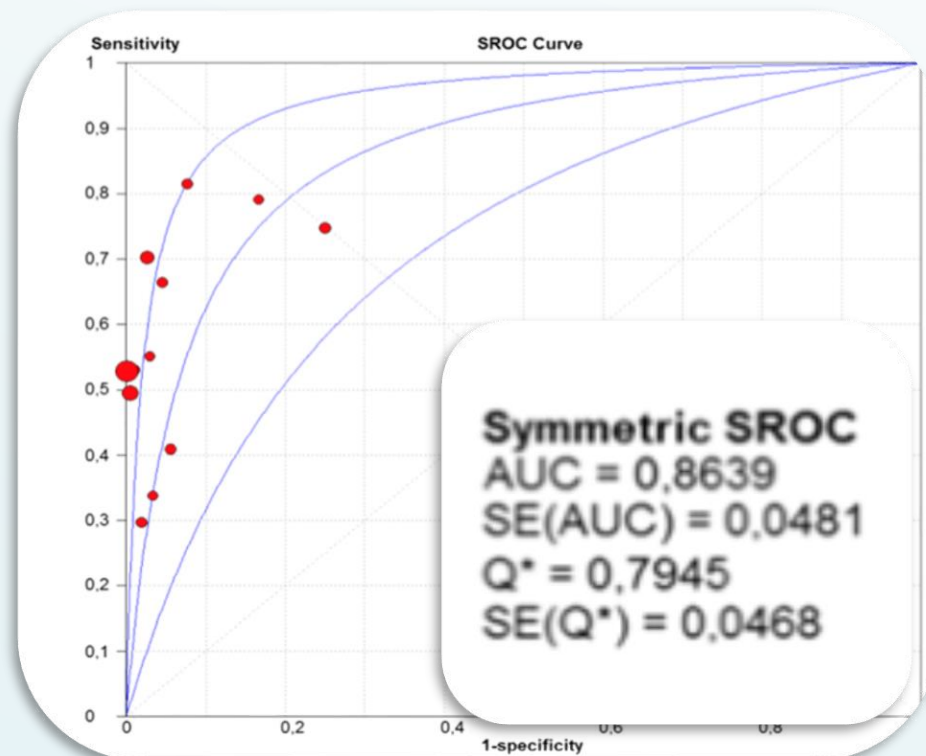
	PAS/biopsy	Culture
Sensitivity	84%	56%
Specificity	89%	99%
+ Predictive Value	93.4%	99.4%
- Predictive Value	75.4%	52%
Accuracy	85.75%	70.3%

Nail clipping with PAS staining is useful to confirm the presence of fungi in the nail plate and its invasion by visualization of fungal structures

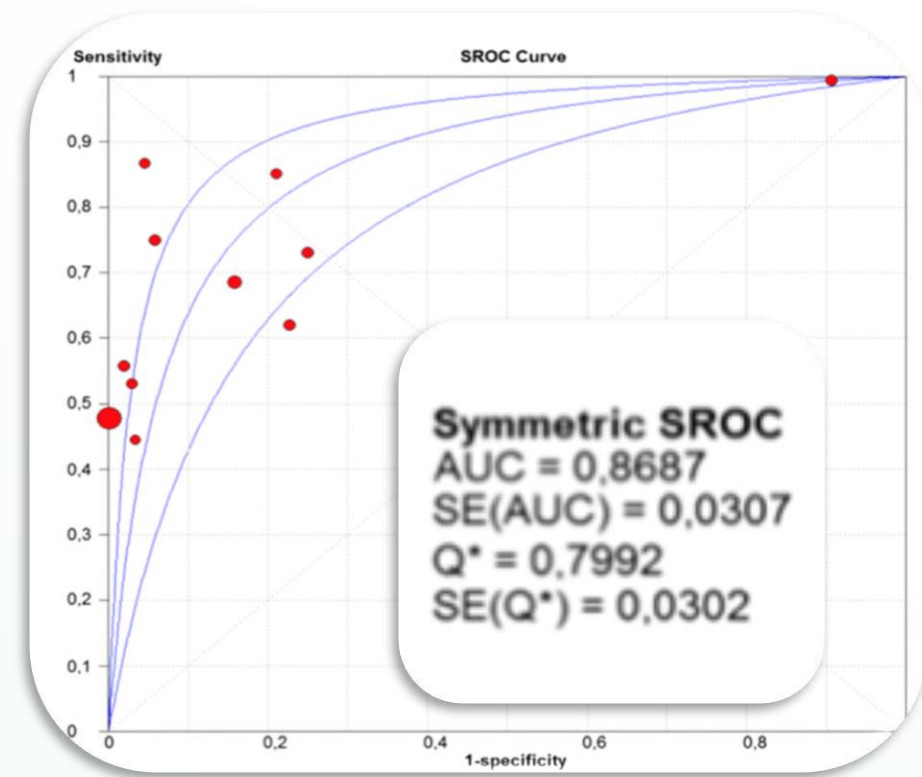
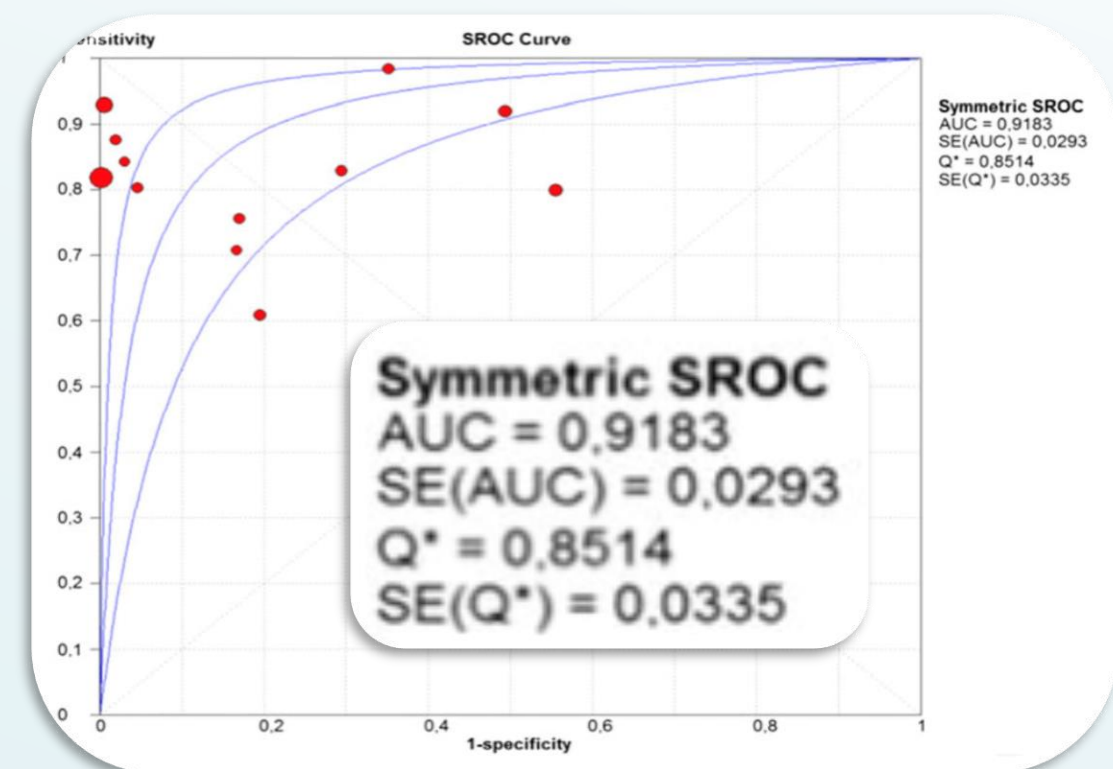
Statistical Analysis *SROC*:

Summary receiver operating characteristics

Culture



PAS Testing



KOH

Why?

No Studies available to Validate OTC topical Toenail medications used in the office

DiNucci Study 2019

Confirm the clinical improvement I experienced with my patients is genuine

Many claims by other Topical OTC meds:
No clinical studies

Met with Dr. Malay and he was able to provide statistical analysis and Research support

How was the study prepared?

Inclusion Criteria:

1. Male or female: 18 - 70 years
3. DSO of at least one of the great toe(s) affecting 25 % to 75 % of the target nail (verified by blinded assessor before randomization)
4. Positive culture for dermatophytes (i.e. Trichophyton species; T. rubrum or T. mentagrophytes)
5. Signed written informed consent

Exclusion Criteria:

1. Proximal subungual onychomycosis
2. DSO of both great toenails where involvement has extended into the proximal portion of the target nail (unaffected proximal nail is less than 2 mm)
3. "Spike" of onychomycosis extending to eponychium of the target nail
4. Presence of dermatophytoma (defined as demarcated and localized thick masses of fungal hyphae and necrotic keratin between the nail plate and nail bed) on the target nail
5. Other conditions than DSO known to cause abnormal nail appearance
6. Topical antifungal treatment of the nails within 1 month before screening
7. Systemic use of antifungal treatment within 3 months before screening
8. Signs of severe peripheral circulatory insufficiency
9. Immunosuppression
10. Participation in another clinical trial with an investigational drug or device during the previous 4 weeks before screening
11. Known allergy to any of the tested treatment products
12. A pregnancy test indicating pregnancy in a woman of childbearing potential at screening (visit 1)
13. Pre-menopausal (last menstruation \leq 1 year prior to screening) sexually active women who :
 - are pregnant or nursing, are not surgically sterile
 - are of child bearing potential and not practicing an acceptable method of birth control

NO Payments to Patients, No Payments to Myself, Free product given to Patients

DiNucci Study 2019

32 patients

20 female (62.5%) | 12 male (37.5%)

2 (NIDDM)

Ave age 64.6 y/o (39 – 86)

20 pos PAS (62.5%), 12 neg PAS (37.5%)

No KOH or Cultures:

Only PAS at National Podiatric Path. Lab

Consecutive patients

No exclusion for % involvement,
Age, Disease, Tinea

Toenail Debridement allowed by patient

Primary Aim

To record the effect of a low surface tension topical medication with antifungal and cosmetic properties on consecutive patients presenting with Toenail dystrophy in both PAS positive and PAS negative patients.

Secondary Aims

Evaluate the safety and tolerability of TAS in patients with toenail dystrophy

Evaluate nail specific changes pre and post treatment



Research Data

Toenail involvement and morphology

Accurate Measurements of toenail

Digital Photos

Caliper measurements of nail thickness

Independent grading of toenails

Specific nail data

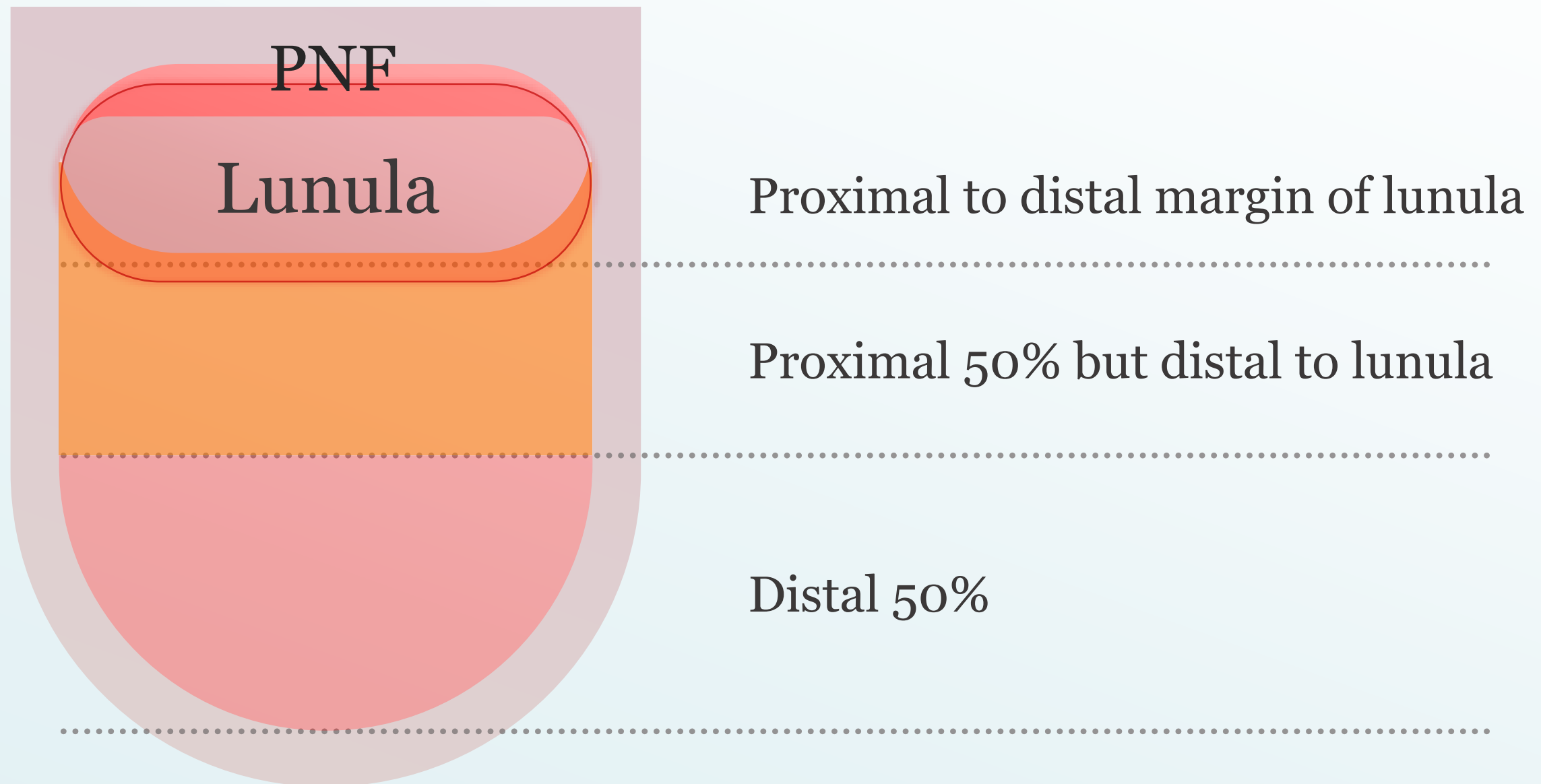
Nail Plate Involvement Score

Inter-rater $r =$
0.9263

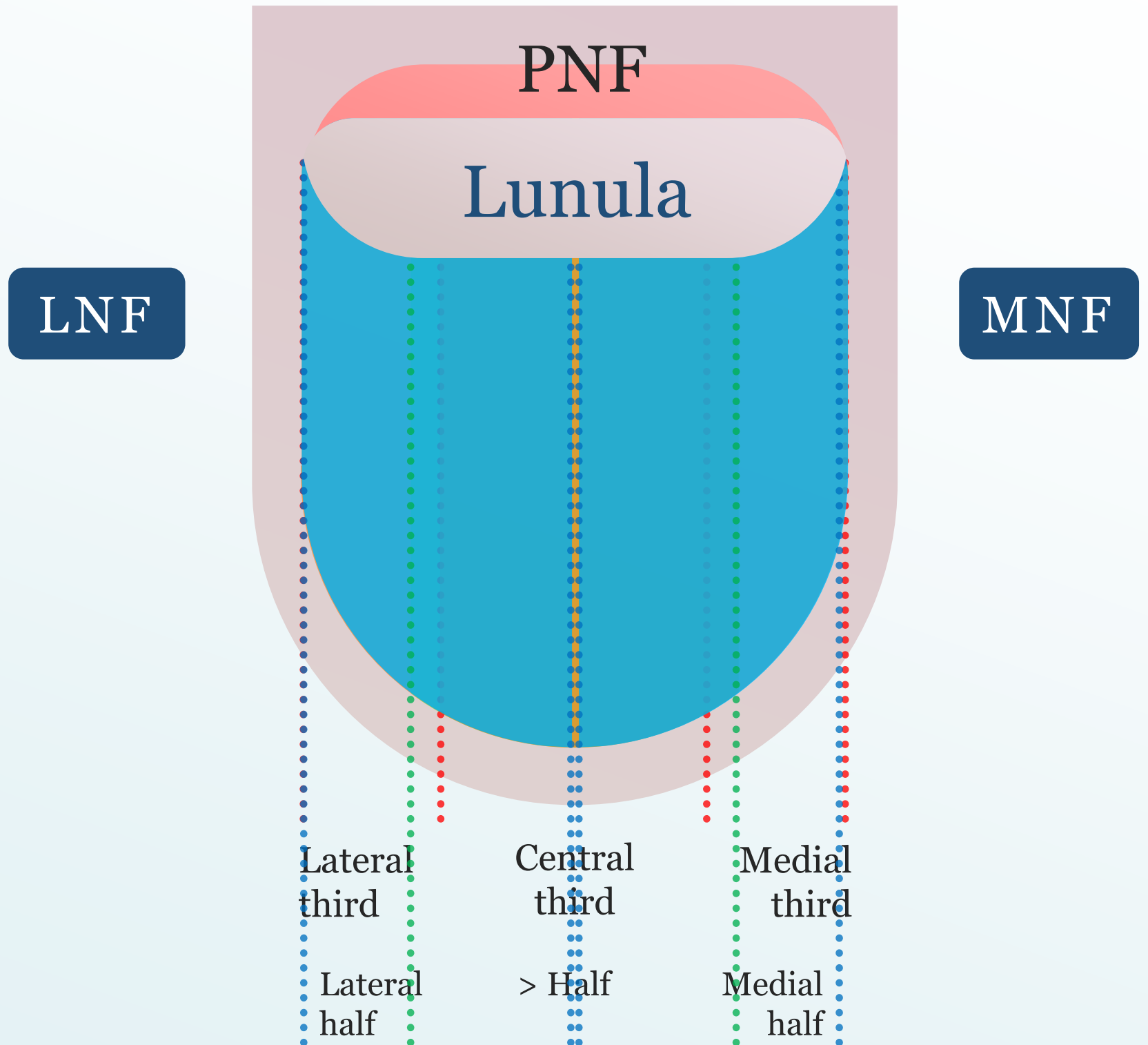
Intra-rater $r =$
0.8988

Nail plate characteristics		Point/s	Sum
Classification of onychomycosis	White superficial	1	
	Distal subungual	2	
	Proximal subungual	3	
Longitudinal segmental involvement of visible nail plate	≤ Distal half	1	
	> Distal half, excluding lunula	2	
	Extending proximal to lunula	3	
Transverse segmental involvement of visible nail plate	≤ Medial third	1	
	≤ Lateral third	1	
	≤ Central third	1	
	≤ Medial half	2	
	≤ Lateral half	2	
	> 50% of total	3	
Proportion of visible nail plate involved (1 to 100%)		1-100	
Shape of visible nail plate	Normal flat/mild curvature	0	
	Grossly thickened, gryphotic, lytic	1	
	Koilonychia/dorsal concavity	1	
	Lytic/arcuate/pincer	2	
	Onychauxis, clubbed	3	
	Ram’s horn	3	
	Longitudinal streak/patch (dermatophytoma)	3	
	Split/canaliformis	4	
Thickness of distal margin of visible nail plate and bed attached to plantar surface of nail plate (mm)	≤1	0	
	>1 to ≤ 2	1	
	>2 to ≤ 3	2	
	>3	3	
	Actual		
TOTAL			

Longitudinal Segmental Involvement



Transverse Segmental Involvement





Normal with flat to
mild dorsal curvatures



Grossly thickened,
incurvated or arcuate



Pincer



Koilonychia or
dorsal concavity



Ram's horn or
gryphotic



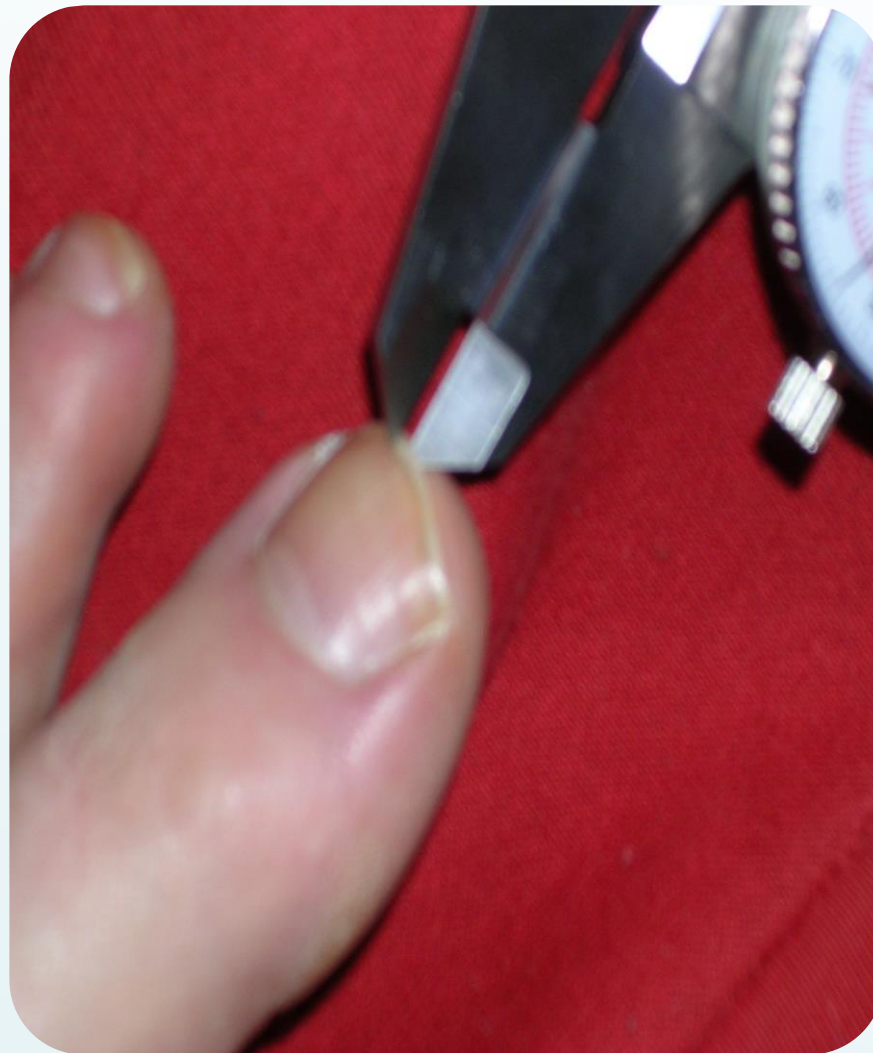
Split or
canaliformis

Specific nail data



Digital caliper

Specific nail data



Thickness (mm) at
grossly thickest site

Specific nail data



Photo Board

Complications/Side effects

No patients required
discontinuation of the treatment.

2 patients described skin irritation which
resolved after education about appropriate
application and use of the medication.

Retrospective case series

(N = 44 nails in 28 patients)

- › One practitioner, consecutive patients
- › Blind outcome assessors
- › Nail involvement determined using highly reliable clinical assessment tool (Spearman's inter-rater $r = 0.9093$, intra-rater $r = 0.9255$)
- › 6-month follow up data
- › 4 (12.5%) patients lost to f/u (2 at random, 2 traumatic nail injuries)
- › Paired Student's t-tests (continuous numeric data) or Wilcoxon signed ranks tests (categorical data) used to compare outcomes
- › Statistical significance defined at the 5% ($p \leq 0.05$) level

Results

N = 44 nails in 28 patients, mean age 65.53 yrs., BMI 28.53 ± 5.6

In the case series, there were:

12 (42.8%)
males

16 (57.2%)
females

2 (7.14%)
31-50 years

5 (17.8%)
51 to 60 years

11 (39.2%)
61 to 70 years

10 (31.2%)
> 70 years

1 (3.57%)
Asian

2 (7.14%)
Black/African American

25 (89.2%)
White race

Results

N = 44 nails in 28 patients, mean age 65.53 yrs., BMI 28.53 ± 5.6

In the case series, there were:

2 (7.14%) Underweight	6 (21.4%) Normal weight	10 (31.2%) Overweight	10 (31.2%) Obese patients
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13 (46.4%)
bilateral cases

15 (53.5%) One nail	11 (39.2%) Two nails	2 (7.14%) Three nails
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Involvement Variable		Baseline	3 Mo	6 Mo
Classif. Score		2 (2,2)	2 (2,2)	2 (2,2)
P-Value	B vs. 3-mos	0.655		
	3 vs. 6-mos		0.655	
	B vs. 6-mos	0.4142		
Long. Involvement		2 (1,2)	2 (1,2)	2 (1,2)
P-Value	B vs. 3-mos	0.3448		
	3 vs. 6-mos		0.2043	
	B vs. 6-mos	0.6371		

Inv Variable		Baseline	3 Mo	6 Mo
T-V Involvement		3 (2,3)	3 (2,3)	3 (1,2)
P-Value	B vs. 3-mos	0.329		
	3 vs. 6-mos		0.071	
	B vs. 6-mos	0.054		
Shape Score		0 (0,1)	1 (0.1)	0 (0, 0)
P-Value	B vs. 3-mos	0.845		
	3 vs. 6-mos		0.002	
	B vs. 6-mos	0.008		

Inv Variable		Baseline	3 Mo	6 Mo
Thickness score		2 (1,2)	1 (1,1)	1 (0,1)
P-Value	B vs. 3-mos	0.035		
	3 vs. 6-mos		0.034	
	B vs. 6-mos	0.008		
Percent Inv		35 (25,60)	32.5 (16.5, 60)	22.5 (10, 60)
P-Value	B vs. 3-mos	0.4238		
	3 vs. 6-mos		0.004	
	B vs. 6-mos	0.025		

Inv Variable		Baseline	3 Mo	6 Mo
Overall Improvement Score		42 (26.5, 71)	40.5 (24.5, 72)	31 (17, 70)
P-Value	B vs. 3-mos	0.415		
	3 vs. 6-mos		0.002	
	B vs. 6-mos	0.027		
PAS +		1(0,1) [19(67.86%)]	0 (0,1) [12 (44.44%)]	0 (0,0) [6 (21.43%)]
P-Value	B vs. 3-mos	0.0143		
	3 vs. 6-mos		0.0143	
	B vs. 6-mos	0.0005		

Discussion:

6 mo. Preliminary results

Statistically significant changes

Baseline - 3 mos	Between 3 - 6 mos	Baseline - 6 mos
——	Shape score	Shape score
Thickness	Thickness	Thickness
——	Percentage inv.	Percentage inv.
——	Overall inv.	Overall inv.
PAS changes	PAS changes	PAS changes

Discussion:

6 mo. Preliminary results

Baseline:

19 of 28 patients positive fungal [(+) PAS]

3 Mo Follow-up:

7/19 (Baseline 36.8% reduction in +PAS)

PAS (-) Toenails 7 patients | PAS (+) Toenails 12 patients

6 Mo Follow-up:

13/19 (Baseline 68.4% reduction in +PAS)

PAS (-) Toenails 13 patients | PAS (+) Toenails 6 patients

Discussion:

6 mo. Preliminary results

Mycologic Cure*:
At 3 mos. 7/19 or 36.8%

Mycologic Cure*:
At 6 mos. 13/19 or 68.4%

* This study reports the results of clinical improvement for both Fungal and Non-fungal toenails.
It also reports the cure rate for Onychomycosis which is considered an off-label use.

Next Steps:

Onychomycosis: Phase III study

Randomized, double-blinded, multi-site, FDA registered trial. Determine the efficacy of Topical Tolcylen vs. placebo in the treatment of mild to moderate Onychomycosis

Principle investigator:
Scott Malay DPM, FACFAS



Observations

- › Cannot predict Mycotic vs non-Mycotic toenails
- › Toenail shape and dystrophy can improve with eradication of infection
- › Patients prefer topical to oral medication



Patient A Baseline



Patient A 6 mo.

Here are All 28 patients:

- › Full transparency of Patient's clinical changes
- › Baseline to 6 mos.
- › Independently graded at different times and intervals



Baseline
Patient B

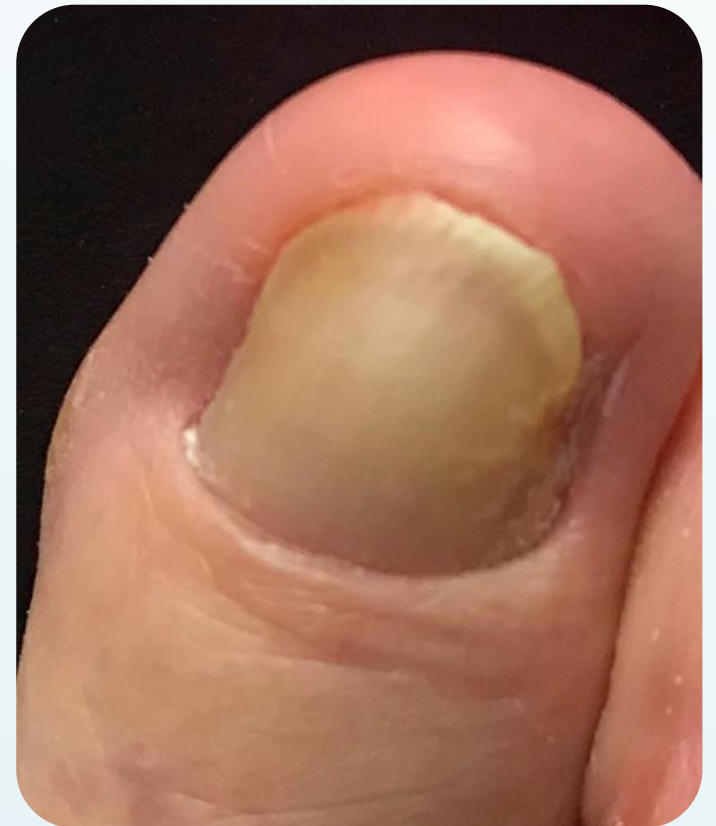


6 Mos
Patient B

Baseline
Patient C



6 Mos
Patient C



Baseline
Patient D



6 Mos
Patient D



Baseline
Patient E



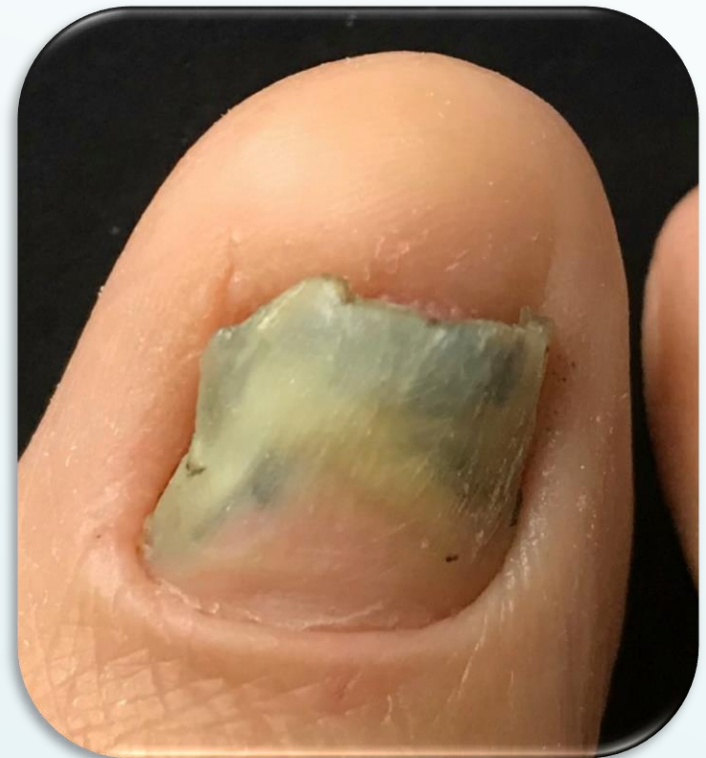
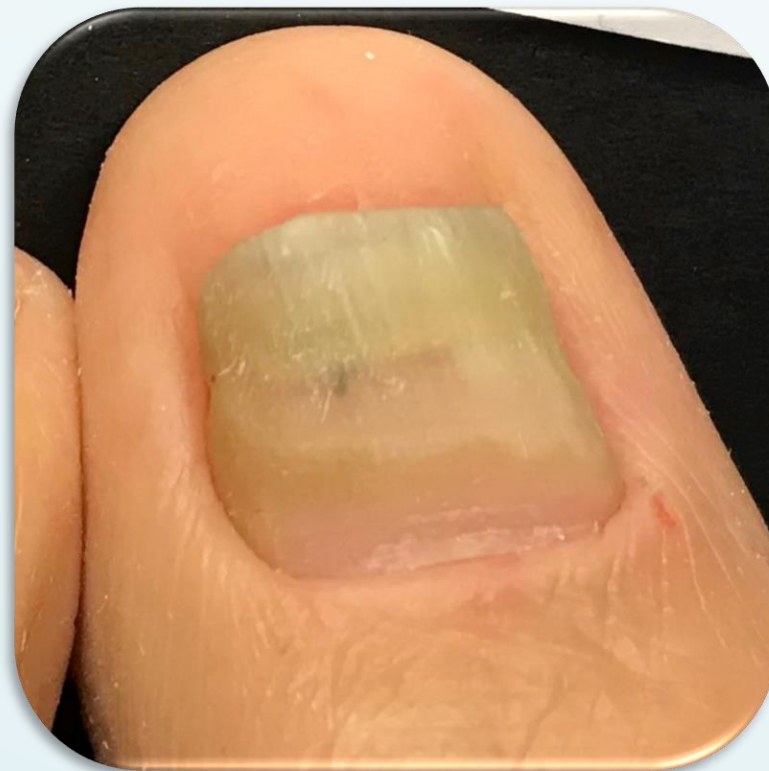
6 Mos
Patient E



Baseline
Patient F



6 Mos
Patient F



Baseline
Patient G

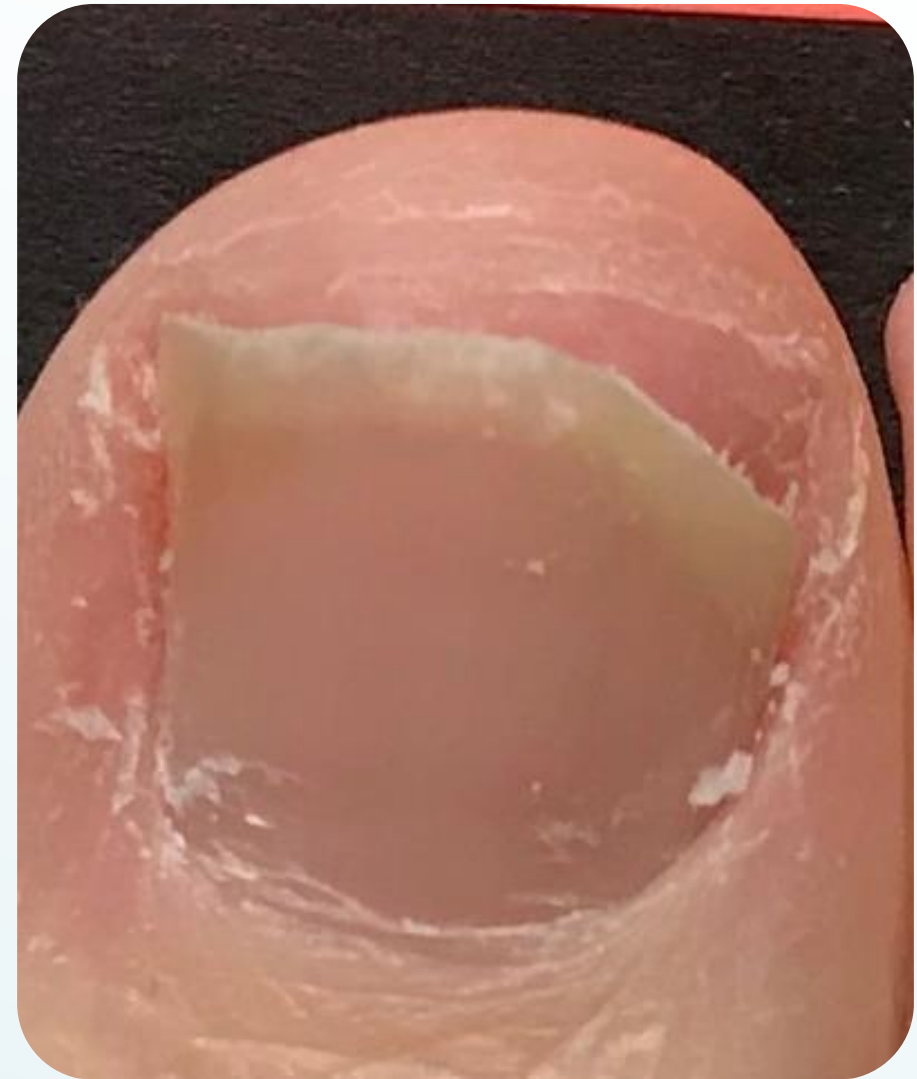


6 Mos
Patient G





Baseline
Patient H



6 Mos
Patient H

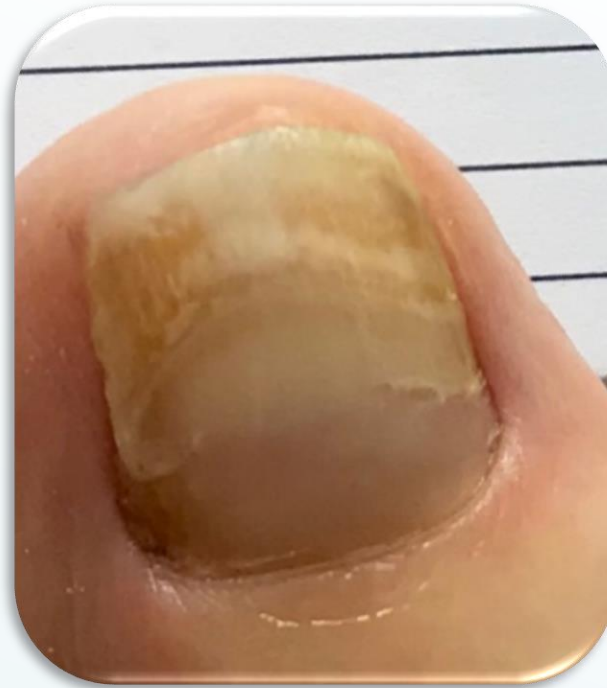


Baseline
Patient I



6 Mos
Patient I

Baseline
Patient J



6 Mos
Patient J



Baseline
Patient K



6 Mos
Patient K





Baseline
Patient L



6 Mos
Patient L



Baseline
Patient M



6 Mos
Patient M

Baseline
Patient N



6 Mos
Patient N



Baseline
Patient O



6 Mos
Patient O



Baseline
Patient P



6 Mos
Patient P



Baseline
Patient Q



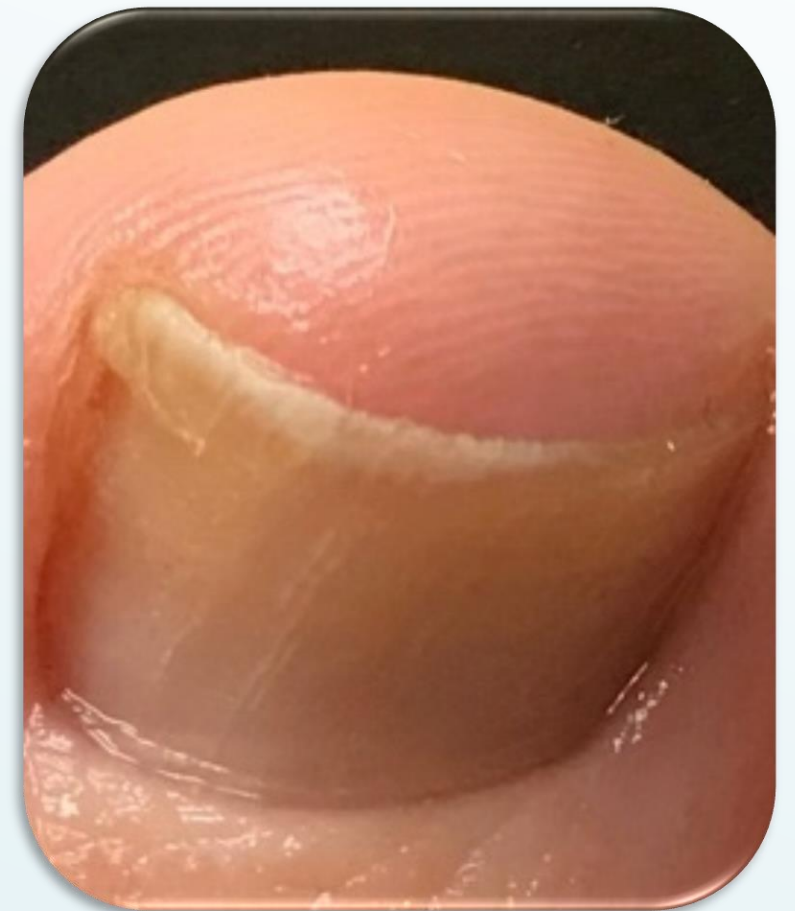
6 Mos
Patient Q



Baseline
Patient R



6 Mos
Patient R





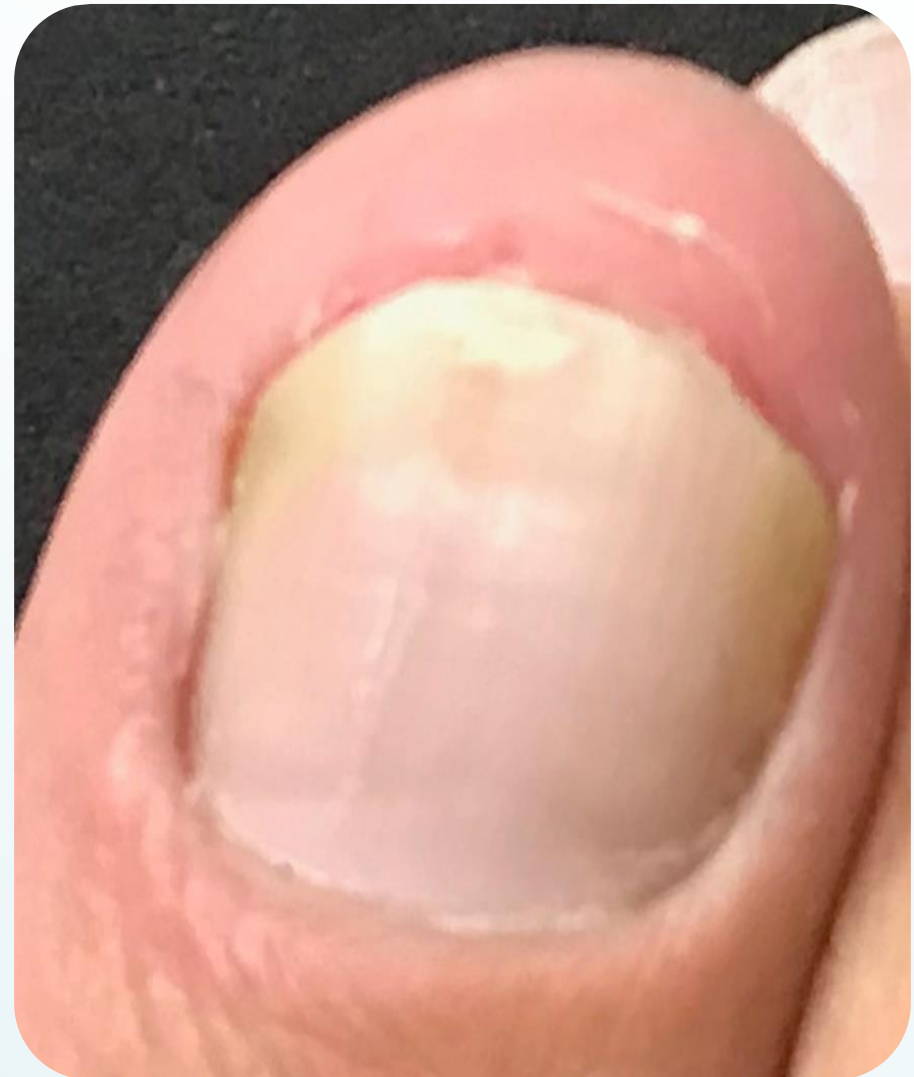
Baseline
Patient S



6 Mos
Patient S



Baseline
Patient T



6 Mos
Patient T



Baseline
Patient U



6 Mos
Patient U

Baseline
Patient V



6 Mos
Patient V



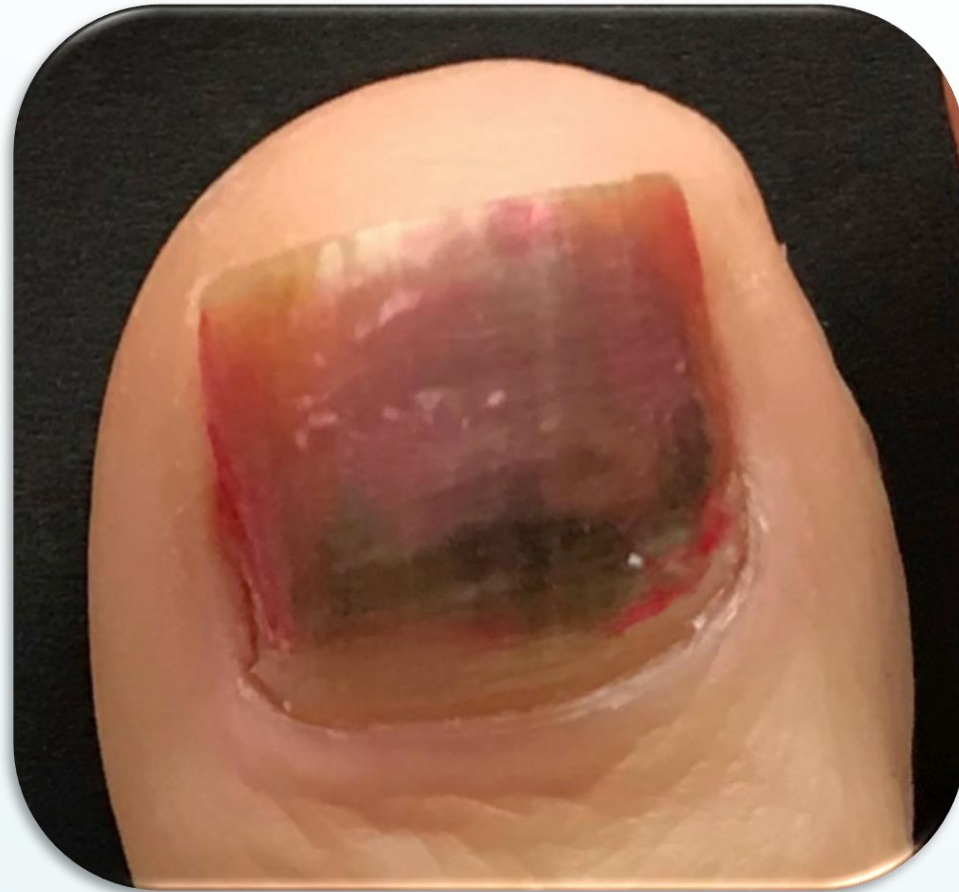


Baseline
Patient W

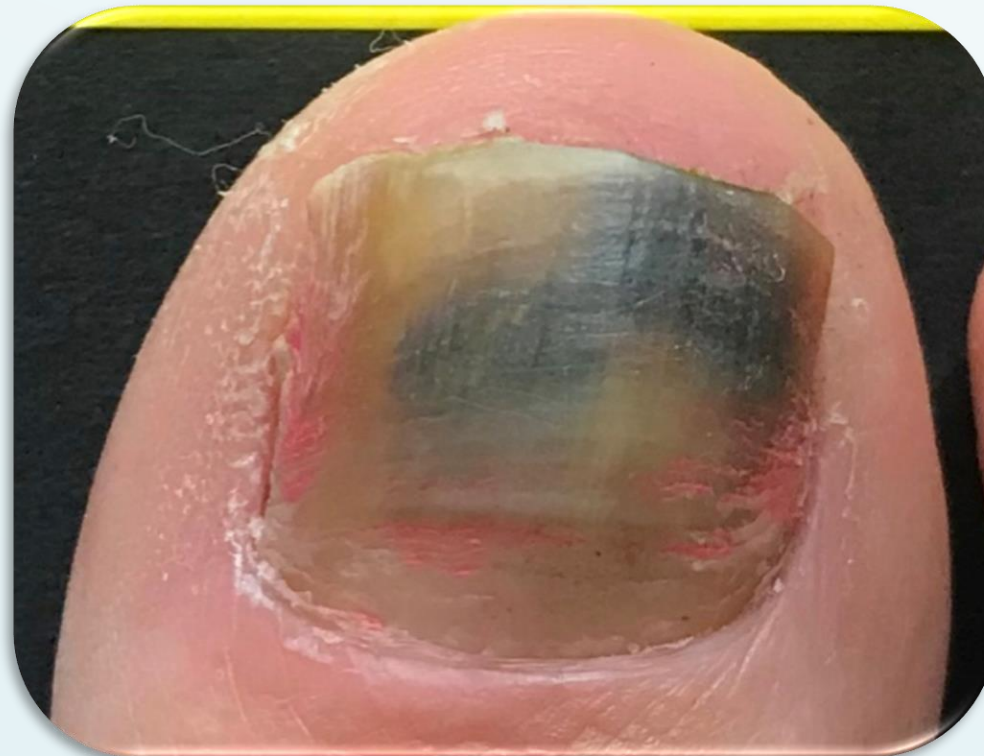


6 Mos
Patient W

Baseline
Patient X



6 mos
Patient X





Baseline
Patient Y



6 mos
Patient Y



Baseline
Patient Z



6 Mos
Patient Z



Baseline
Patient AA



6 mos
Patient AA



Baseline
Patient BB



6 mos
Patient BB