Light at the end of the toenail

Reflections on a 3-year longitudinal study of light therapy for severe onychomycosis and future applications to wound care

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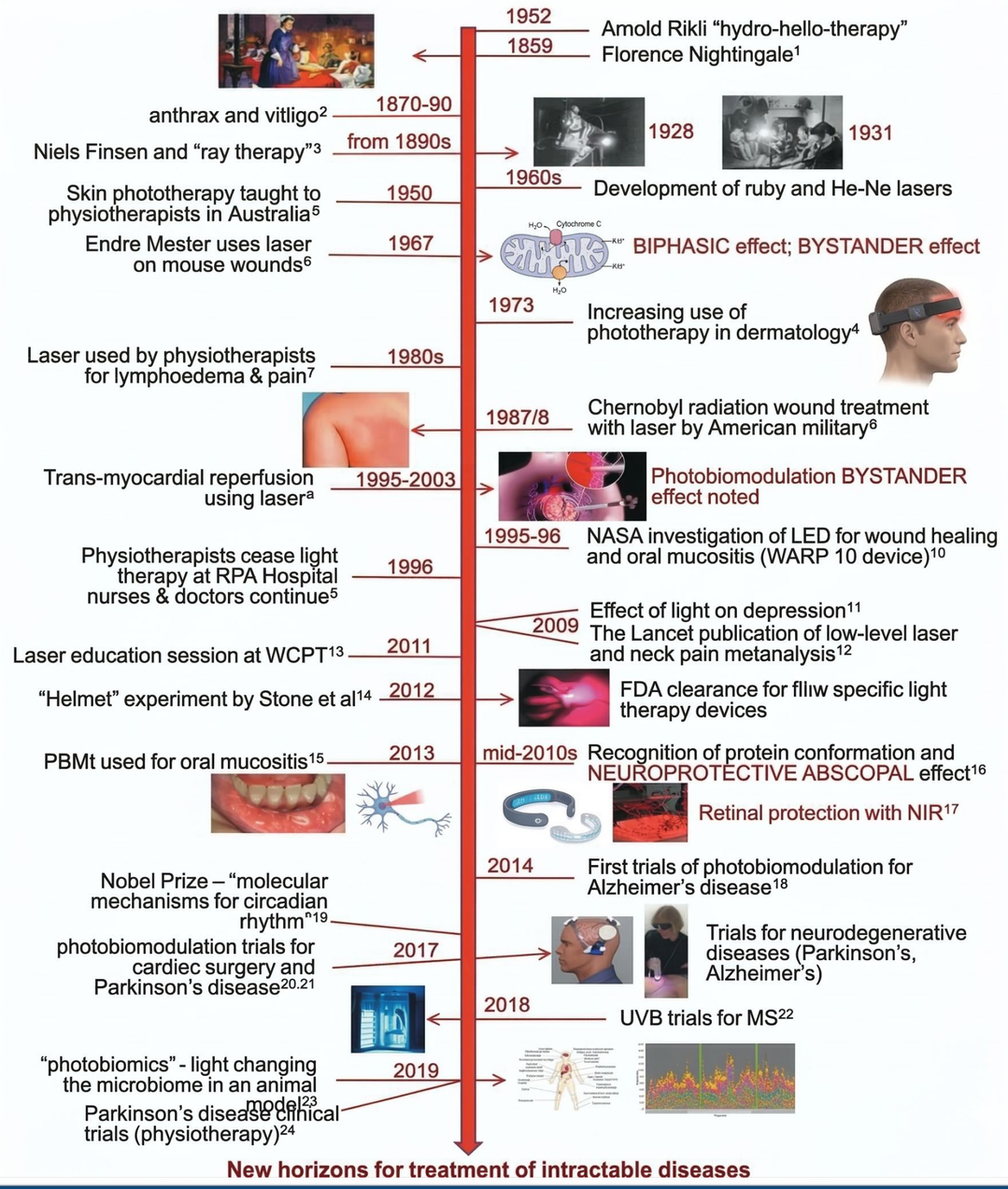
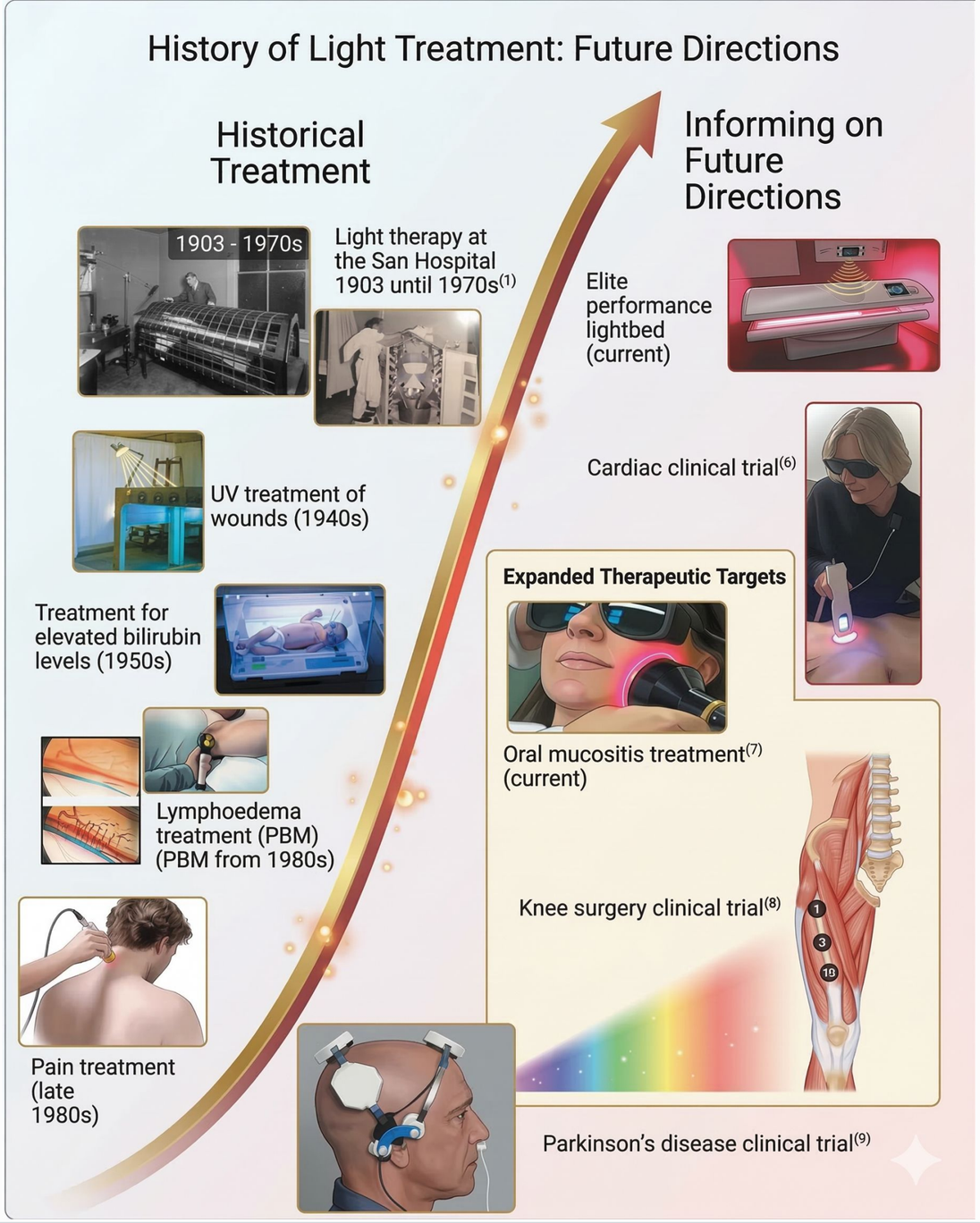
Outline

1. Background
2. Study Aim
3. Methodology
4. Results
5. Discussion
6. Conclusion

History of Phototherapy



History of Phototherapy – Future Directions



History of Phototherapy – Future Directions

MEDICAL APPLICATIONS OF PHOTODYNAMIC THERAPY (PDT)

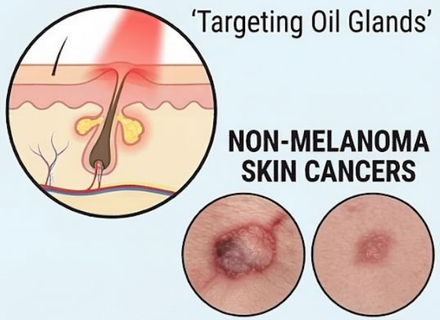
Sensitizer + Light + Oxygen = Cell death

1. DERMATOLOGY: TARGETING PRE-CANCERS & SKIN CONDITIONS

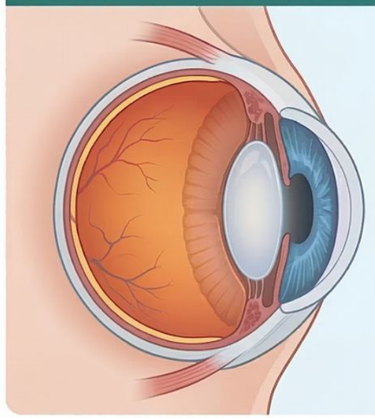
Example A: ACTINIC KERATOSIS
(Pre-Cancerous lesions)

'Pre-Treatment' 'Post-PDT'

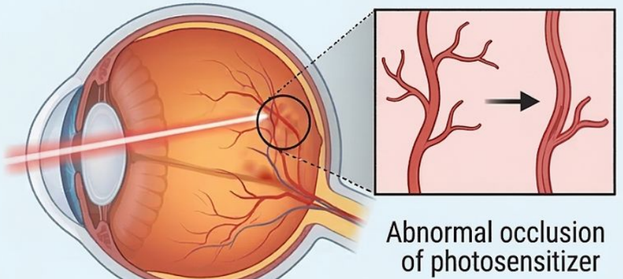
Example B: SEVERE ACNE



3. OPHTHALMOLOGY: AGE-RELATED MACULAR DEGENERATION (AMD)



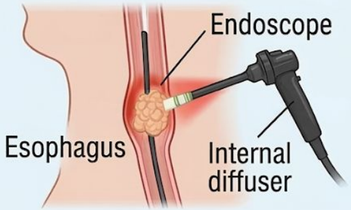
Example: WET AMD (using **VERTEPORFIN**)*



Preserving vision by closing leaking vessels.

2. ONCOLOGY: TREATING CANCERS & PALLIATIVE CARE

Example A: ESOPHAGEAL CANCER*



Often used for palliative care/early-stage tumors.

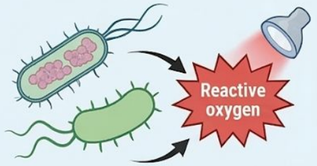
Example B: LUNG CANCER*

Fiber optic light, obstructing tumor

Example C: BLADDER CANCER*

4. ANTIMICROBIAL: COMBATING RESISTANT INFECTIONS

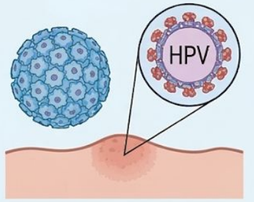
Example A: BACTERIAL INFECTIONS*



Antibiotic-resistant bacteria (like MRSA)

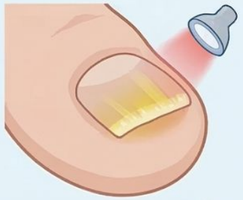
Alternative for antibiotic resistance.

Example B: VIRAL INFECTIONS*



Human Papillomavirus & cutaneous wart

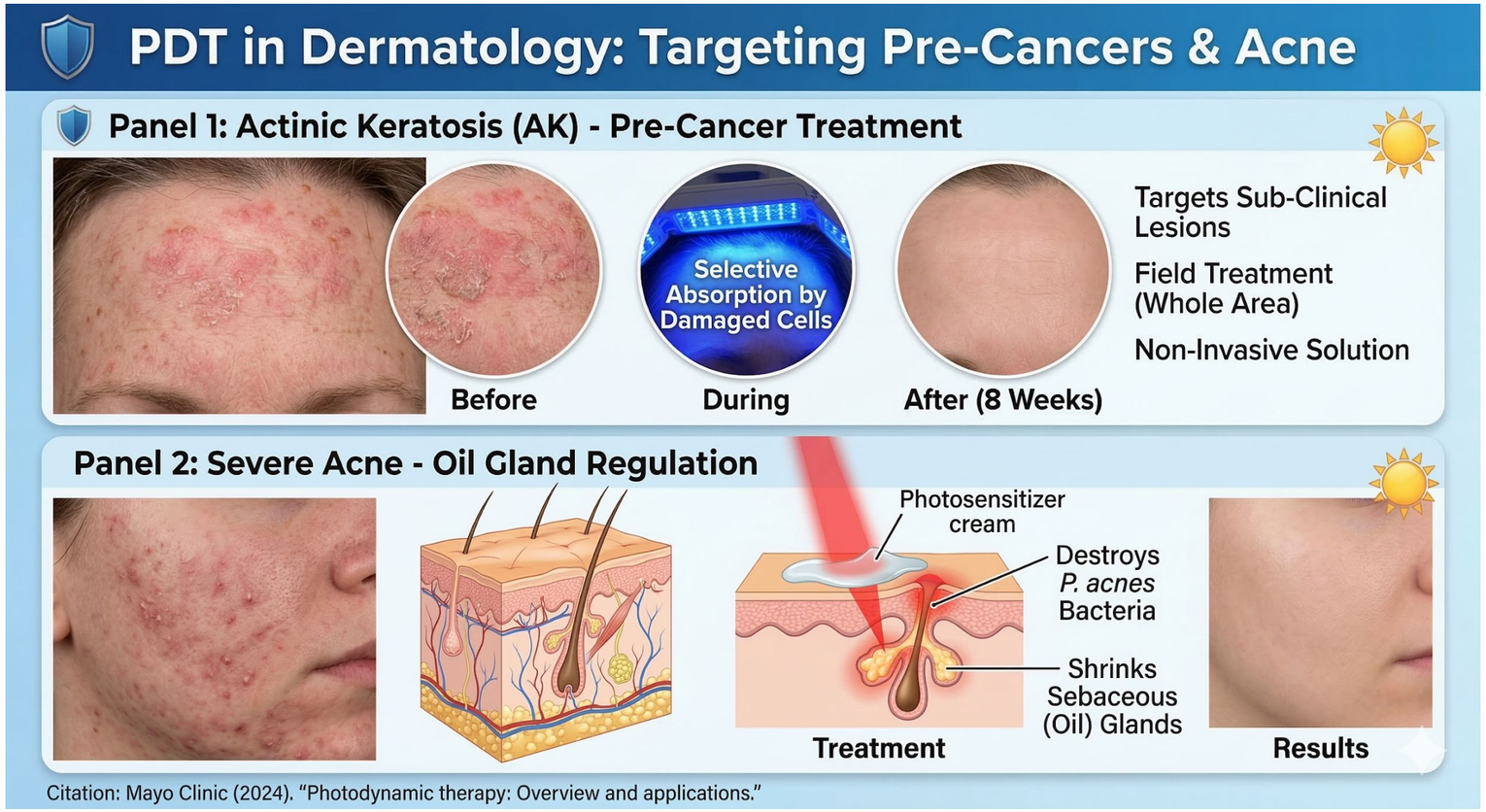
Example C: FUNGAL INFECTIONS*



Toenail fungus (Onychomycosis)

Citation: Mayo Clinic (2024). "Photodynamic therapy: Overview and applications."

PDT in Dermatology: Targeting Pre-Cancers & Acne



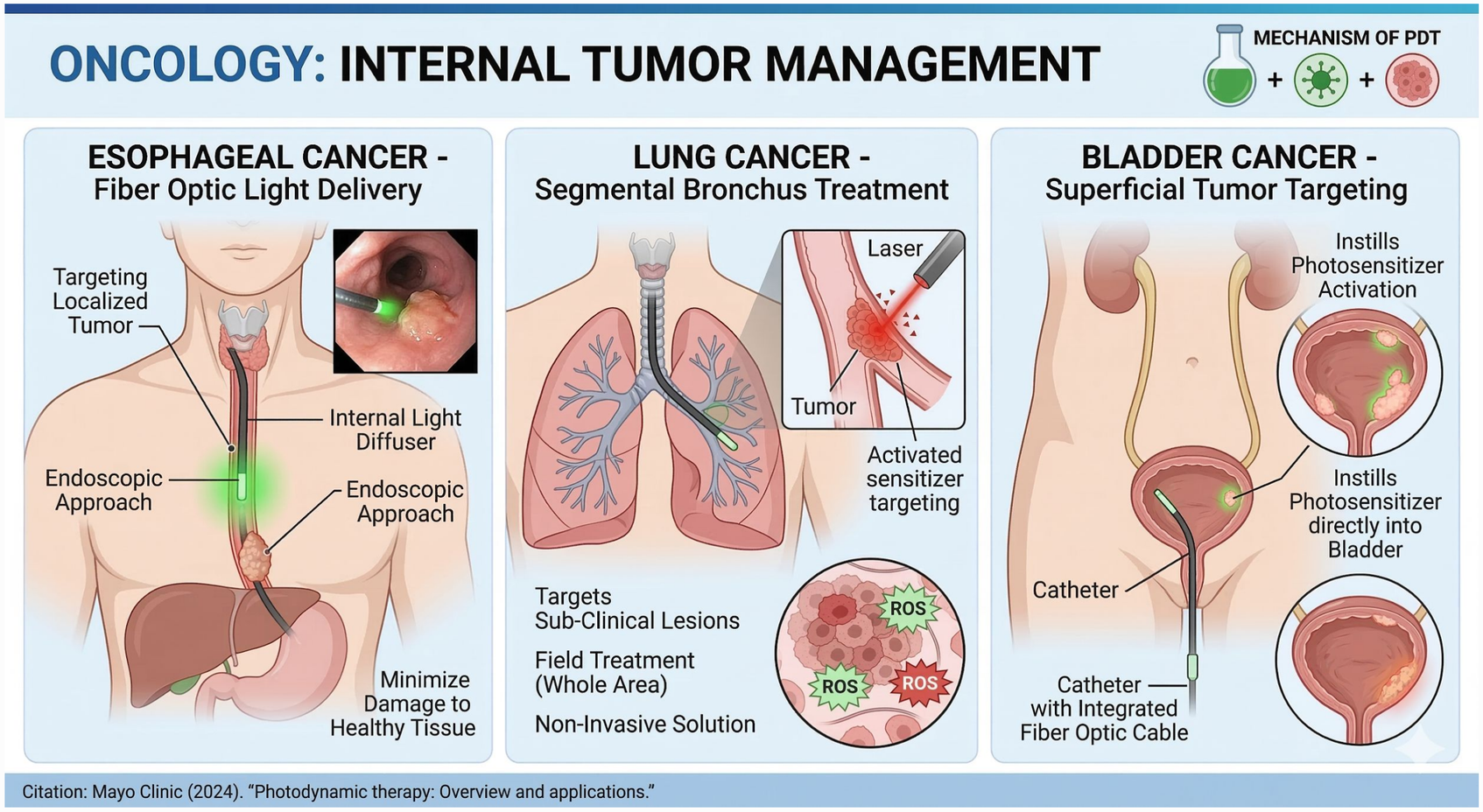
- **Actinic Keratosis (AK):** Treats the entire "field" of sun damage, destroying invisible pre-cancerous cells before they become malignant.
- **Severe Acne:** Selectively destroys sebaceous (oil) glands and kills *P. acnes* bacteria without systemic drugs.
- **Non-Melanoma Skin Cancers:** A non-surgical option for superficial Basal Cell Carcinoma, offering superior cosmetic results (no scarring).
- **Visual Suggestion:** Place the "Pre-Treatment" vs. "Post-PDT" images here.
- **Citation:** *Mayo Clinic (2024). "Photodynamic therapy: Overview and applications."*

PDT in Oncology: Internal & Palliative Care

Esophageal Cancer: Uses an endoscope to deliver light to tumors, helping patients regain the ability to swallow.

Lung Cancer: Clears obstructed airways in patients with non-small cell lung cancer using fiber-optic diffusers.

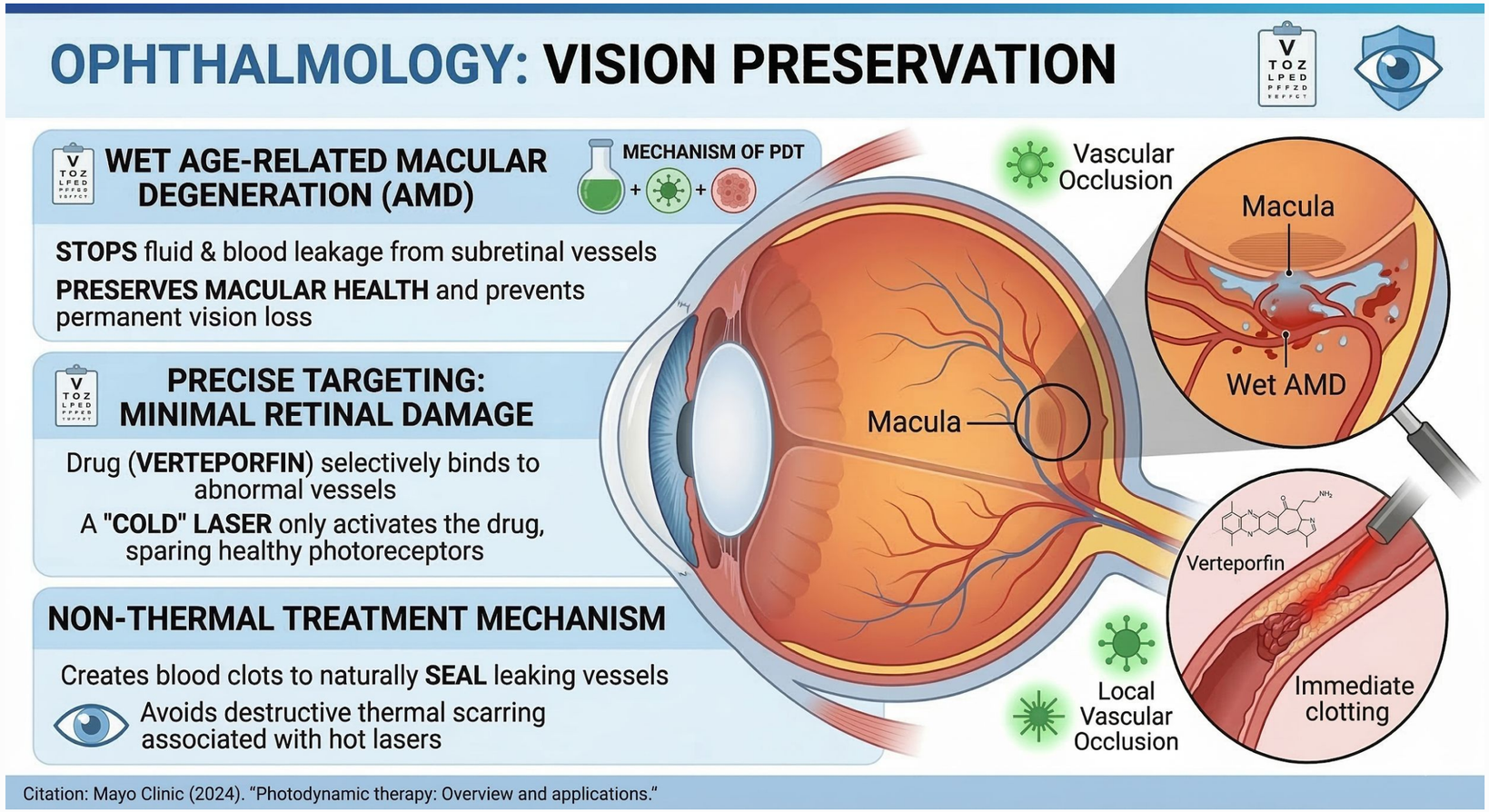
Bladder Cancer: Instills photosensitizers directly into the bladder to treat early-stage, superficial tumors.



Citation: Mayo Clinic (2024). “Photodynamic therapy: Overview and applications.”

PDT in Ophthalmology: Treating Wet AMD

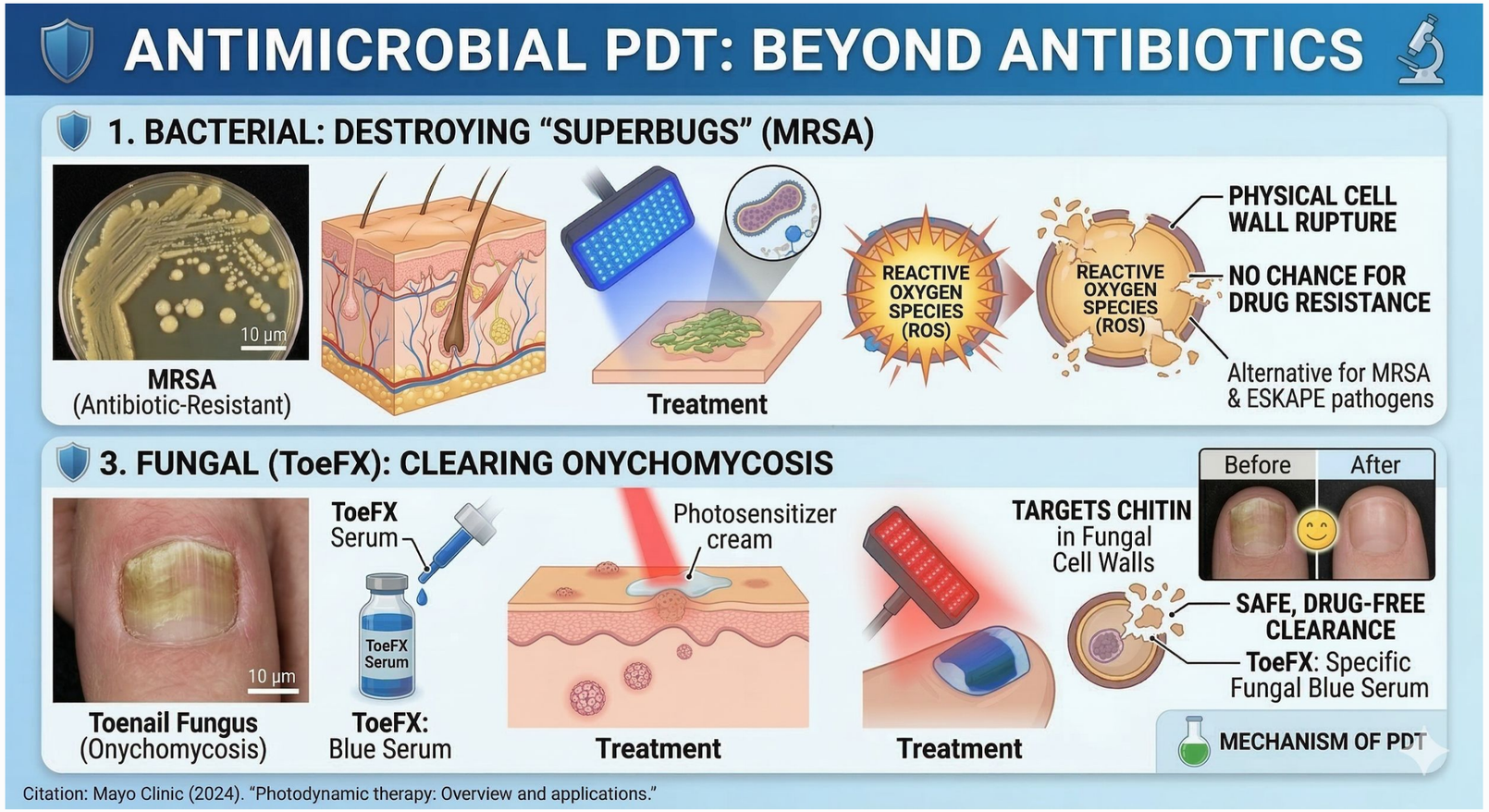
- **Condition:** Used specifically for **Wet Age-Related Macular Degeneration (AMD)**.
- **The Drug:** Patients are injected with **Verteporfin**, which travels to the abnormal blood vessels behind the macula.
- **The Reaction:** A low-energy laser activates the drug, causing the leaking vessels to clot (occlusion) without damaging the retina.



Citation: Mayo Clinic (2024). "Photodynamic therapy: Overview and applications."

Antimicrobial PDT: Beyond Antibiotics

- **Bacterial:** Destroys "Superbugs" like MRSA by physically rupturing cell walls; no chance for drug resistance.
- **Viral:** Effectively treats warts and lesions caused by the Human Papillomavirus (HPV).
- **Fungal (ToeFX):** Uses a specialized blue serum to target fungal cell walls in nails (Onychomycosis) without liver toxicity.



Citation: Mayo Clinic (2024). “Photodynamic therapy: Overview and applications.”

The Latest on Phototherapy Onychomycosis

Distal-lateral subungual

Dermatophytomas (deep longitudinal infection, hard to reach)

Total dystrophy

Most severe form

Proximal subungual

Rare

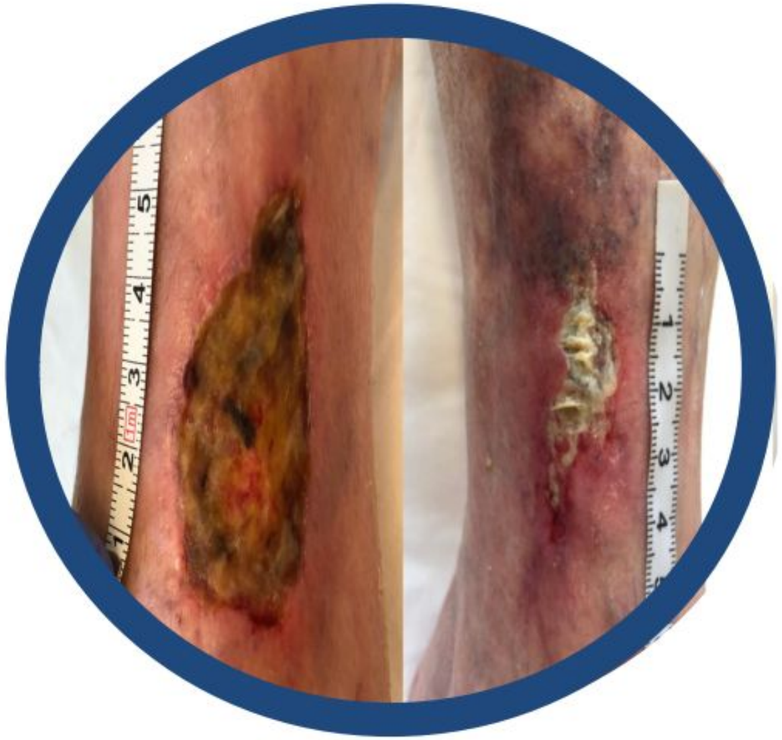
Superficial white

Less severe

Challenges in Treating Severe Cases

- Most studies do not focus on severe infections
- Severe infections are challenging due to nail thickening and consequent difficulty in reaching the infection underneath the nail plate
- The nail matrix may be damaged, reducing the capability of healthy growth, even if the infection is eradicated

Wound care: future application



Photodynamic Therapy for the Treatment of Infected Leg Ulcers - A Pilot Study Krupka et al. *Antibiotics* 2021, *10*(5), 506;

Redefining the Chronic-Wound Microbiome: Fungal Communities Are Prevalent. Kalan et al. *mBio* 2016, 7(5), e01058-16

ONYCHOMYCOSIS TREATMENT OPTION LANDSCAPE

	 EFINACONAZOLE	 TERBINAFINE (ORAL)	 LASER	 LIGHT THERAPY
Compliance	Daily for 48 weeks	Daily over 12 weeks + blood tests	Varies with laser	Done at the clinic
Side Effects	Low	Liver toxicity scares many patients	Some burning sensation	None
Efficacy	15-18% complete cure	46% complete cure	Inconsistent	73% (>3 mm clear nail or complete clearance)
ROI	None	None	Variable	High

Close-up on Severe Onychomycosis

1. Aging

2. A self-perpetuating cycle

(the worse it is, the worse it gets)

Close-up on Severe Onychomycosis

Aging

Decrease peripheral circulation

- Poor blood flow reduces immunity and nutrients.

Weakened immune response

This compromised immunity allows fungal organisms to spread deeper into the nail matrix and nail bed, leading to more severe manifestations of onychomycosis.

Slower nail growth - Harder to see results

Close-up on Severe Onychomycosis

Self-perpetuating cycle

“The worse it is, the worse it gets”
In severe onychomycosis, the fungal organisms produce keratinases and other enzymes that degrade keratin, allowing fungal colonization and the subsequent breakdown of nail architecture. Keratin breakdown weakens the nail plate, facilitating even deeper fungal penetration.

Immune response has a downside
Localized inflammation occurs in response to fungal colonization, leading to thickening of the nail and surrounding tissues (onychauxis). The chronic inflammatory state contributes to nail dystrophy and further weakens the structural integrity of the nail plate.

Slower nail growth
This provides a favorable environment for fungal persistence. The fungus can proliferate in the nail plate for extended periods before natural shedding can eliminate the infection.

Study Aim

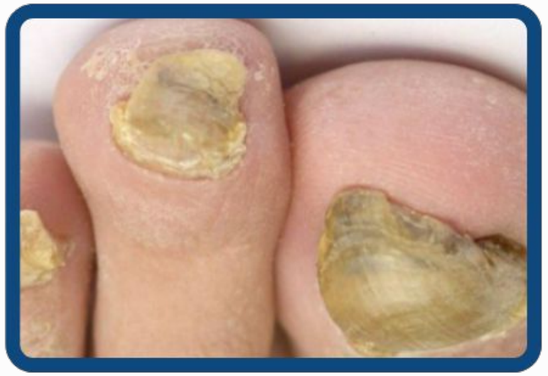
- Evaluate the safety and efficacy of a novel light therapy for severe onychomycosis, including totally dystrophic nails

- Included “non-model” patients with co-morbidities, who are often excluded

- Light Therapy for Onychomycosis Study — Pilot Study of ToeFX Light Therapy Device for Distal Subungual Onychomycosis (DSO) of the Toenail. ClinicalTrials.gov identifier: NCT05139888 / Sponsor: ToeFX Inc.
- Efficiency of methylene blue-mediated photodynamic therapy vs intense pulsed light in the treatment of onychomycosis in the toenails” (Alberdi & Gómez, 2018/2019)
- Randomized controlled trial comparing photodynamic therapy based on methylene blue dye and fluconazole for toenail onychomycosis” (Souza et al., 2013)

Unique Aspects of the Study

- Focus on severe cases: totally dystrophic nails and dermatophytomas



- Most studies will exclude these nails
- Longitudinal study design
- Largest longitudinal LED-Based light therapy study conducted to date

Why Light Therapy for Severe Onychomycosis?

Patients with severe onychomycosis may be seniors, who are hesitant to add a terbinafine pill to their regimen or may have difficulties applying local treatments daily for months

Non-toxic, safe

Increasingly many clinicians are embracing the idea of combination therapies for onychomycosis. Light therapy has no pharmaceutical ingredients and may be combined with topicals or orals.

Patient Characteristics

- 101 patients, 165 nails
- Average age: 60 years
- 80% of patients had the infections for 5 years or more
- Three centers, several providers
- Diagnosis confirmed through KOH, culture, and/or PCR

Inclusion/Exclusion Criteria

- **90% of nails had severe infections**
  Nail matrix involvement, dermatophytomas, <2 mm of clear nail

- **Exclusion:** diabetic patients

- **Comorbidities allowed:** heart disease, tinea pedis, psoriasis, cardiovascular issues, poor circulation

Study Sites and Timeline

Hamilton

Langley, British Columbia

Windsor

2020 to 2023

Pre-Treatment Protocol

- **Debridement with high-speed burr**
  - The value of debridement is becoming more prevalent in the literature
  - Studies show that debridement increases the efficacy of topicals and light therapy, and even of oral/systemic drugs

- **Application of topical light-sensitive formula with a strong affinity for fungal microorganisms**

Light Therapy Details

- Red light (660 nm, 0.042 W/cm^2) and Blue Light (410 nm) were applied to the dorsal surface of the foot for 12 minutes
- Bi-weekly treatments
- Strong Light source (no laser/heat generated)

Fungal staining

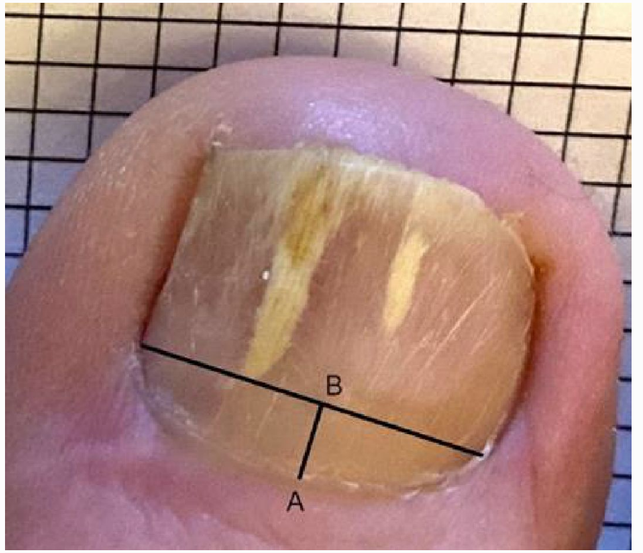
Serum has a strong affinity for fungal organisms. Infected areas turn blue, allowing clinicians to carefully target the infection.

Safety and Side-Effects

- No side-effects reported
- High tolerability, suitable for patients with comorbidities
- Agnostic to the causative agent (effective against all pathogens known to cause onychomycosis)
  - Efficacy of antifungal pharmaceuticals depends on the causative agent, and antifungal resistance to terbinafine is increasing.

Evaluation of Clear Nail Growth

- Photographs taken on a standard piece of graph paper
- Custom software used for accurate nail growth measurement



Success Criteria

- **Primary success:** ≥3 mm of clear nail or total clearance
- **Secondary success:** Mycological cure (negative KOH/culture or two consecutive negative cultures)

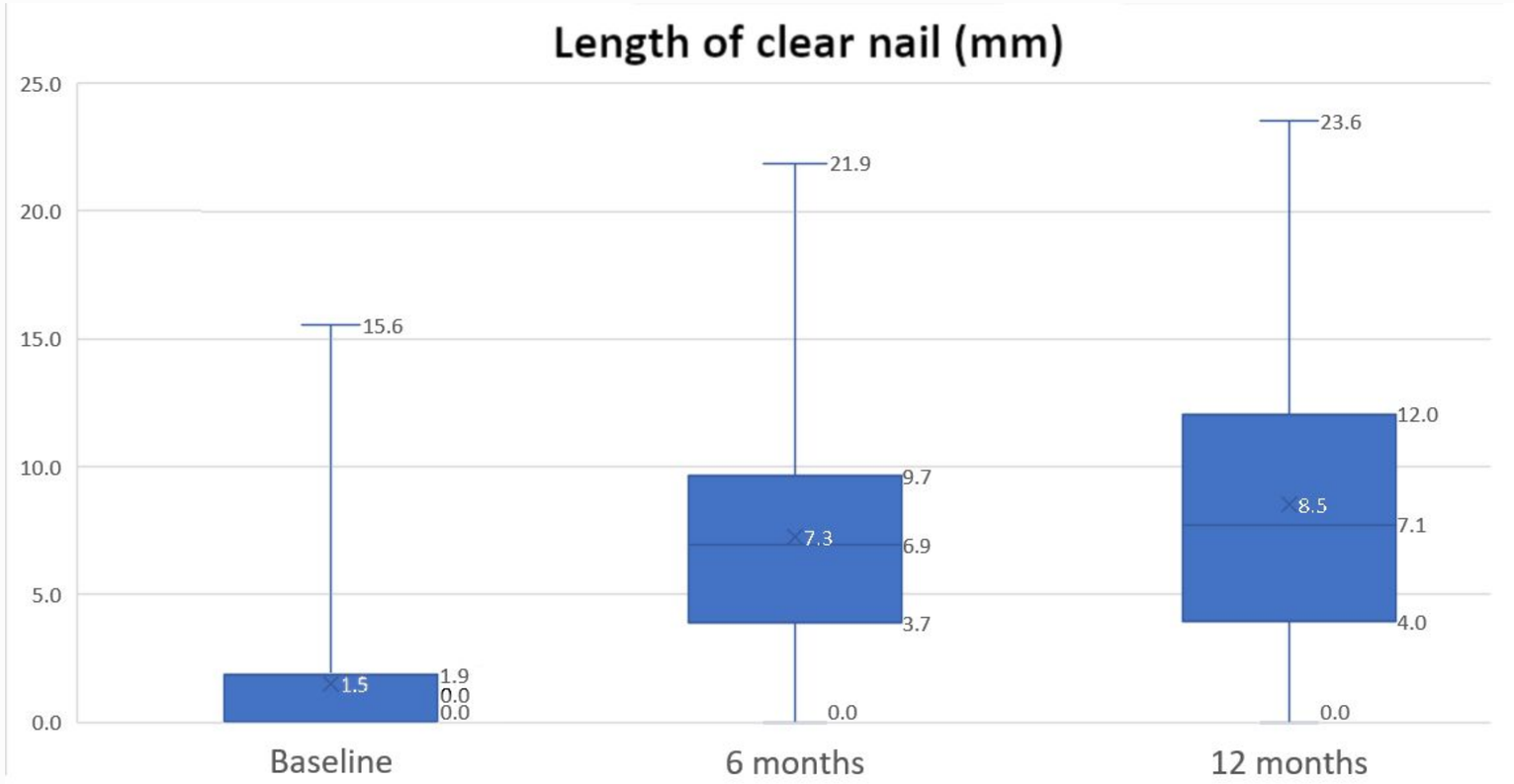
Comparison Methods

- Paired t-tests used to compare growth before and after treatment

- Success goal: ≥50% of treated nails showing clear growth > 3 mm

Success Achieved

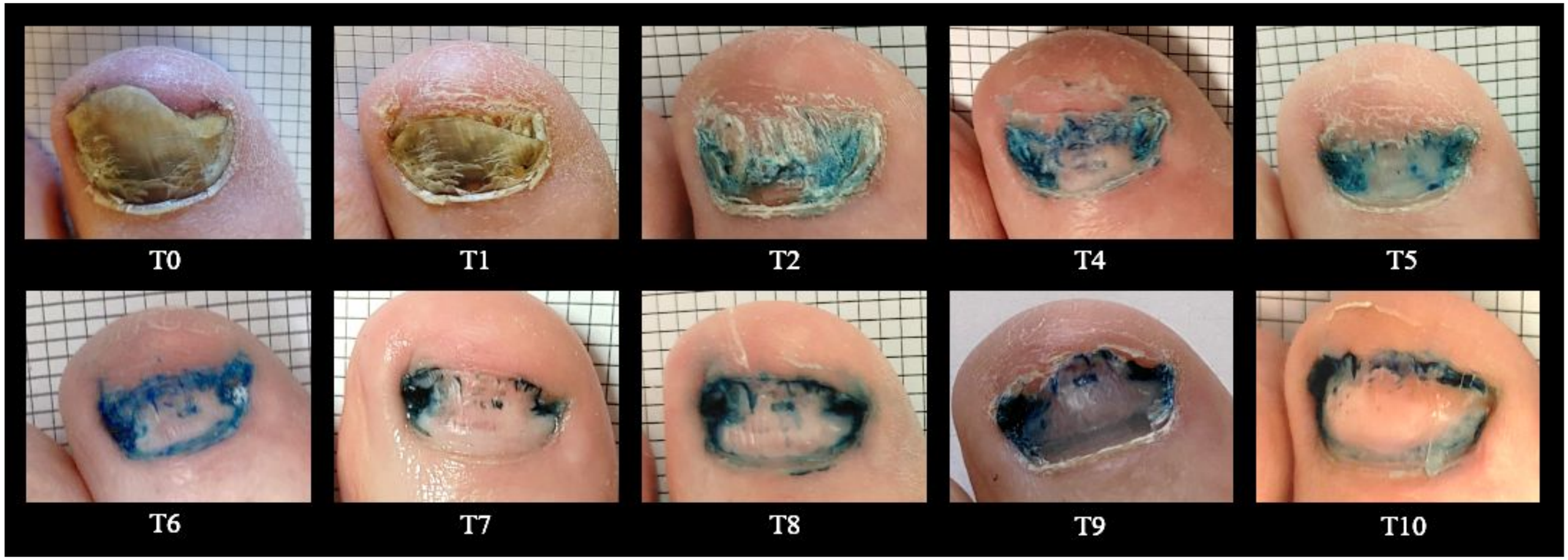
- 73% of nails (120/165) achieved the success criterion (> 3 mm of growth), 53% (88/165) > 6 mm
- Mean growth 5.7 mm (boxes: 1st-3rd interquartiles, line: median, cross: mean, whiskers: total range)



Light Therapy Effectively Reduces Onychomycosis and Promotes Healthy Nail Growth Even in Severely Affected Toenails: A Longitudinal Cohort Study

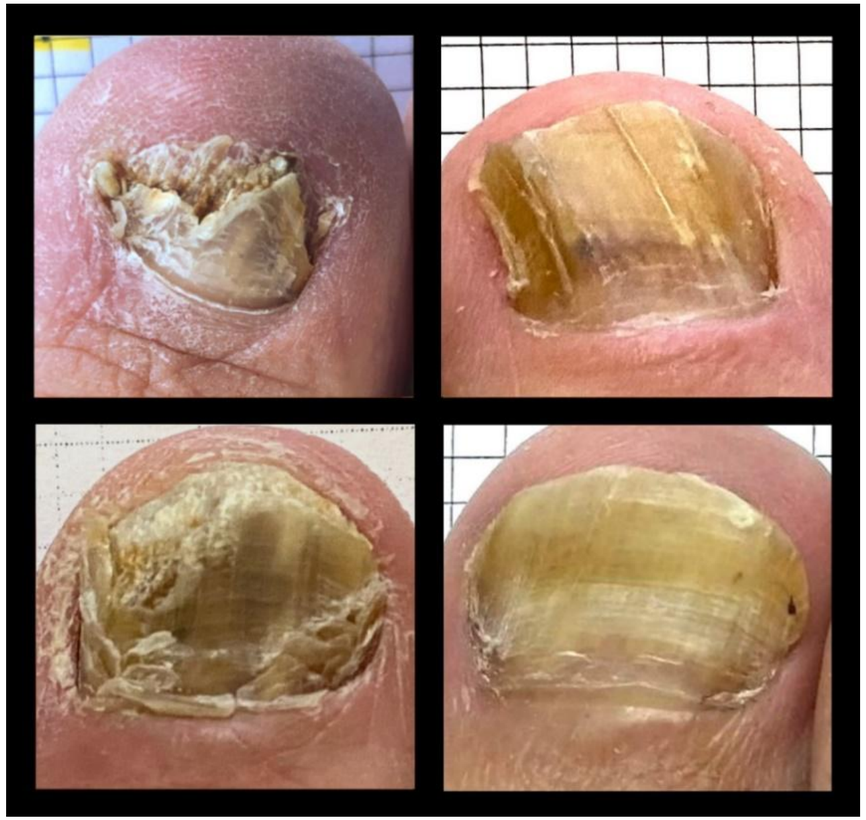
Outcome	Total nails (n = 165)	Mild/moderate infection (≥ 3 mm clear nail) (n = 12)	All severe infections (n = 153)			
			Severe Class I (< 3 mm clear nail) (n = 19)	Severe Class II (dermatophytomas present) (n = 59)	Severe Class III (totally dystrophic) (n = 75)	Total Severe (n = 153)
Any new growth	143 (86.7%)	12 (100.0%)	18 (94.7%)	48 (81.4%)	65 (86.7%)	131 (85.6%)
Growth ≥ 3 mm or total clearance, n (%)	120 (72.7%)	8 (66.7%)	15 (78.9%)	36 (61.0%)	61 (81.3%)	112 (73.2%)
Growth ≥ 6 mm or total clearance, n (%)	88 (53.3%)	7 (58.3%)	10 (52.6%)	28 (47.4%)	43 (57.3%)	81 (52.9%)
No change, n (%)	17 (10.3%)	0 (0.0%)	0 (0.0%)	7 (11.8%)	10 (13.3%)	17 (11.1%)
Decreased healthy nail, n (%)	5 (3.0%)	0 (0.0%)	1 (5.3%)	4 (6.8%)	0 (0.0%)	5 (3.3%)
Mean healthy growth (mm)	5.9 ± 4.5	4.5 ± 4.4	6.7 ± 4.2	5.0 ± 4.6	6.6 ± 4.5	6.0 ± 4.3
Mycological cure* (n = 127 lab results available)	75/127 (59.1%)	5/10 (50.0%)	6/16 (37.5%)	26/46 (56.5%)	38/55 (69.1%)	70/117 (59.8%)

Before and After

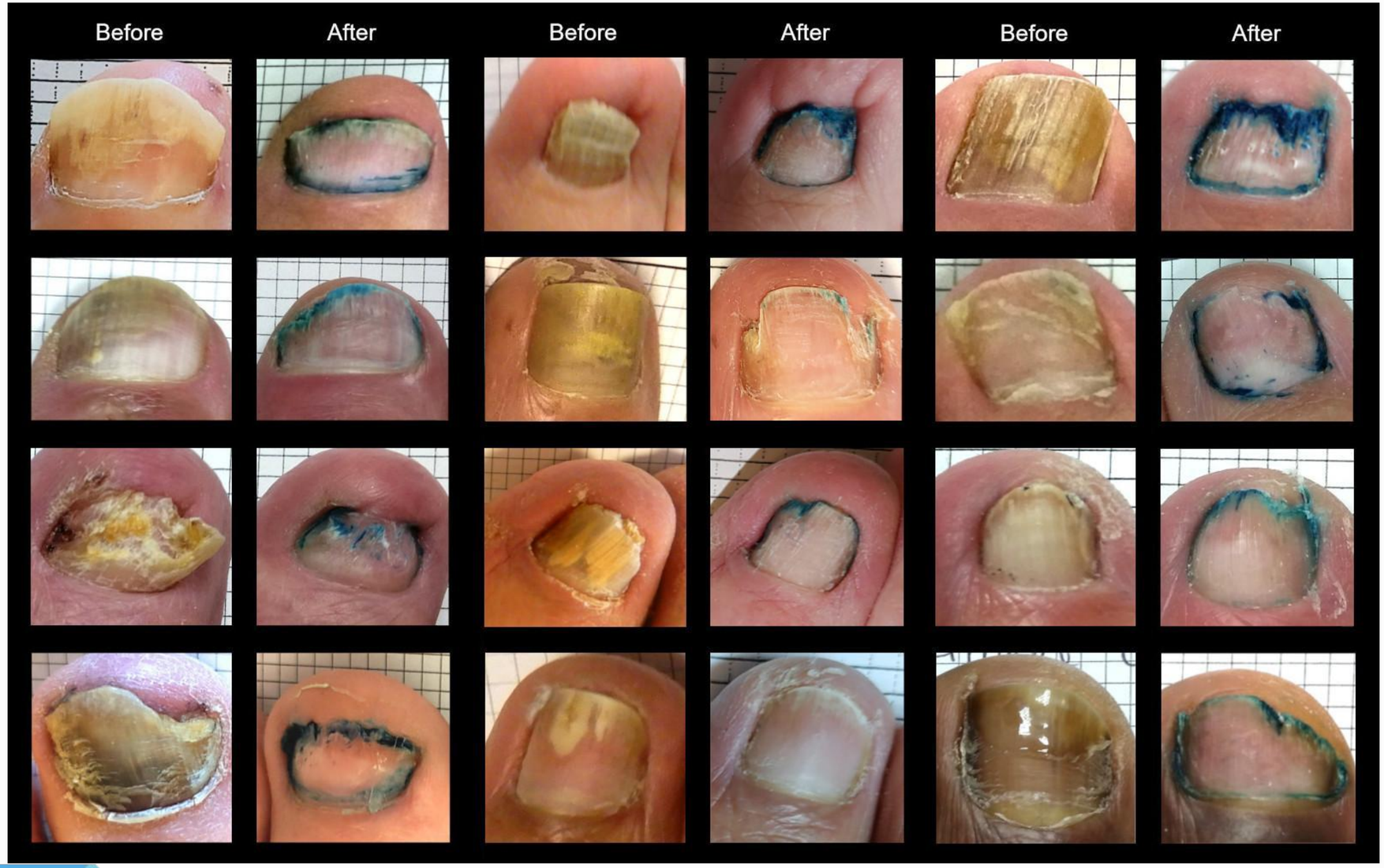


Examples of totally dystrophic (TD) nails

In the current study, 92/217 nails were assessed as “totally dystrophic



Case Studies



Partner Clinic Results

Patient 5

This is a great addition to private practice Advanced Foot Care clinics because it is a tangible and trackable treatment for nail fungus. Its non-toxic and it has a high efficacy. With proper debridement the nail will noticeably repair.

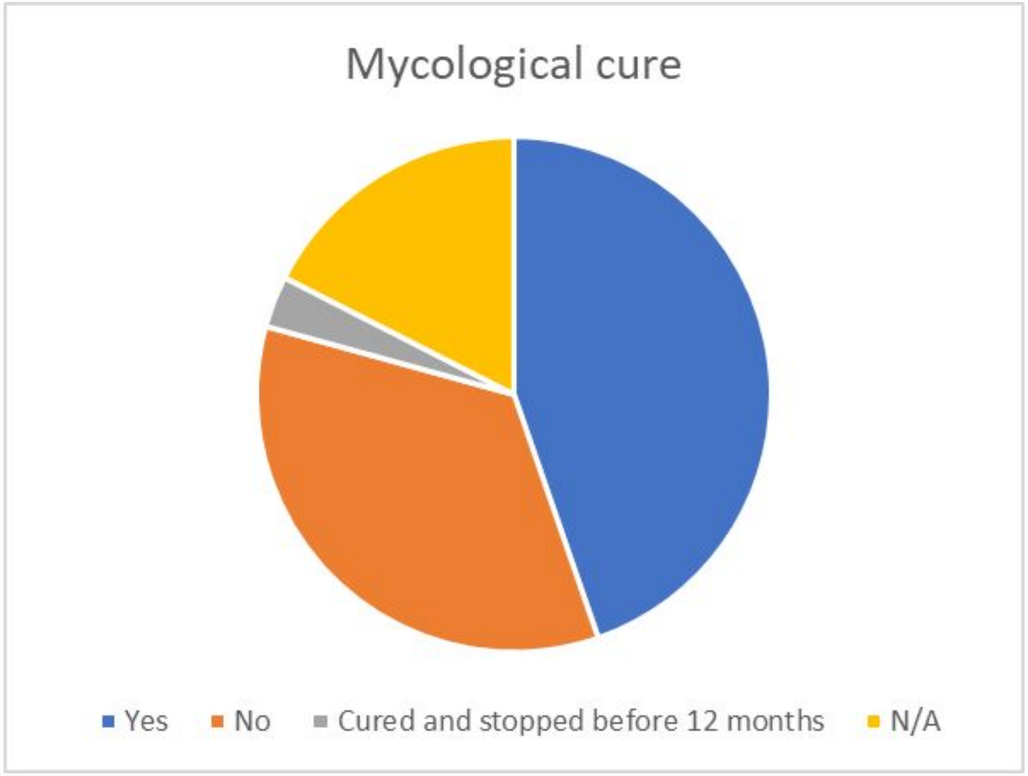
Partner Clinic Results

Patient 5

Now we see after 4 months most of the fungal nail is repaired, new nail is growing in rapidly. We can even see on his second toe that we did some of the deep debridement in the corner to achieve better results with the smaller nail.

Mycological Cure

59% (of available data) achieved mycological cure



(N/A n = 38; yes n = 104, no n = 75, cured and stopped n = 7)

How does this compare to other therapies?

- A study of patients with mild-to-moderate onychomycosis only (no dermatophytomas or matrix involvement) treated with the topical drug Jublia® reported a mycological cure rate of 53.4%-55.2%

- Terbinafine shows the highest mycological cure rates (up to 70% at 48 weeks)

- We report an overall mycological cure of 58.1%,
  - 89% of patients were assessed as severe to extremely severe

How does this compare to other light therapy studies?

- Alberdi et al. (2020) study: compared (MB) and methyl aminolevulinate (MAL) photodynamic therapy (PDT) in mild-to-moderate toenail onychomycosis, showing that MB-PDT led to faster and more sustained improvement in nail condition.

- Souza et al. (2013) study is a randomized controlled trial that compared the efficacy of methylene blue (MB)-mediated photodynamic therapy (PDT) to oral fluconazole in treating toenail onychomycosis. A total of 80 patients were enrolled, with 40 receiving MB-PDT and 40 receiving fluconazole. The MB-PDT group showed a significantly higher clinical cure rate of 90% at 24 weeks, compared to 45% in the fluconazole group ($P < 0.002$).

Next Steps

Combination therapies may be the next frontier in onychomycosis treatments.

Next Steps

Wound care and healing with photodynamic therapy

BEFORE

AFTER 10 DAYS
(3 SESSIONS)

BEFORE

AFTER 9 TREATMENTS

Emerging evidence and clinician reports suggest phototherapy may aid wound and wart management. Images shown are for educational purposes only.

References:

- Minatel DG, et al. Phototherapy promotes healing of chronic diabetic leg ulcers that failed to respond to other therapies. Lasers Surg Med 2009;41: 433-41
- Hassan SNE, et al. Photodynamic therapy using methylene blue and intense pulsed light versus intense pulsed light alone in treatment of verruca: A randomized controlled study. Photodiagnosis Photodyn Ther. 2021;36:102541.

Thank you

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Partner Clinic Results

Patient 4

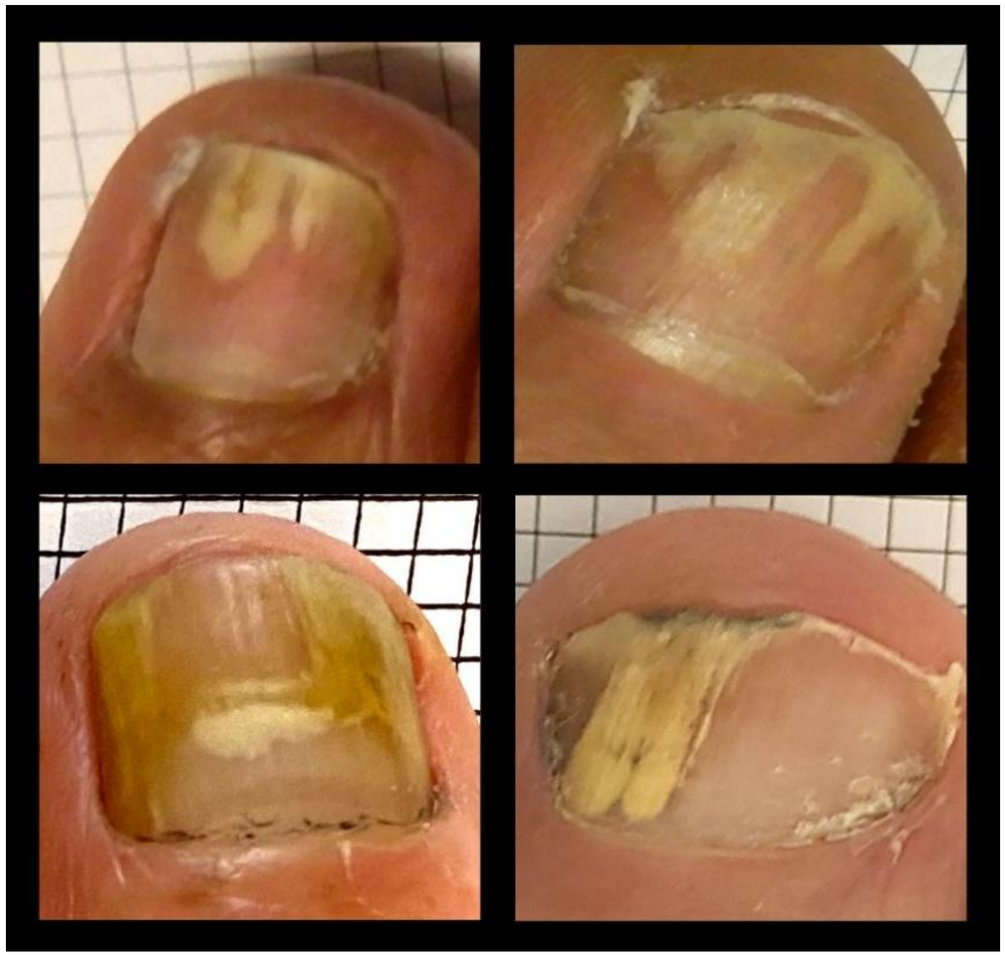
Here is the finishing treatment stage. You can see that the fungal infiltration is all but gone. Nice pink nail bed and no signs of fungal advancement. We still treated this nail till the left-over damaged nail had grown off to completion.

Partner Clinic Results

Patient 5 - 1

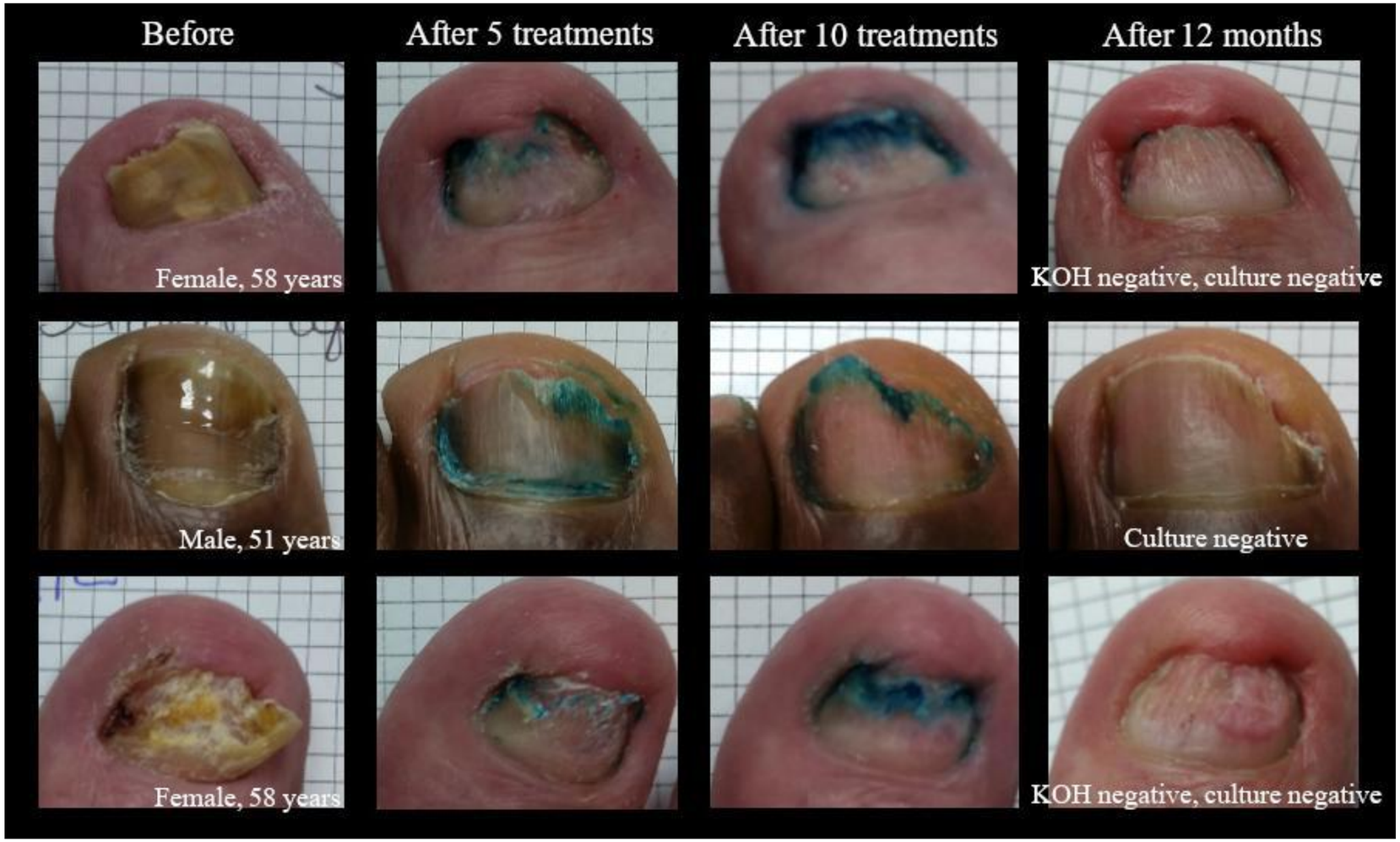
He presented with a massively infiltrated nail. Large thickening throughout and had been dealing with this issue for many years. Local Podiatrist only debrided the nail to make it more comfortable in his shoes.

Examples of nails with dermatophytomas (DPs)



Case Studies

Case Studies



Photodisinfection prevents relapse 86% of the time. Clearer nails will stay clear.