

# Aks and PDT: Where Are We Now?

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# Relevant Disclosures

Consulting honoraria from Abbvie, Allergan, Almirall, Arcutis, Biofrontera, BMS, Castle Bioscience, CMS Aesthetics DCME, EPI Health, Foundation for Research and Education in Dermatology, Galderma, Genentech, Kintor, Lilly, Merz, Nextphase, Novartis, Ortho Dermatologics, Pharmatecture, Pierre Fabre, Plasmed, Prolacta Bioscience, Pulse Biosciences, Regeneron, Skinceuticals/L'Oreal, Sun Pharma, UCB, and Verrica.

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# Clinical Challenges in AK PDT

- Pain
- Consistency
- Adverse Effects
- Patient Acceptance
- Seasonality
- Light Source and Sensitizer
- Prevention of Progression
- Recurrence

# FDA APPROVED ALA PREPARATIONS AND VEHICLES

## 20% ALA Solution in Alcohol

Requires mixing ethanol and ALA powder, must be used within 2 hours

Indicated for face or scalp, or upper extremities

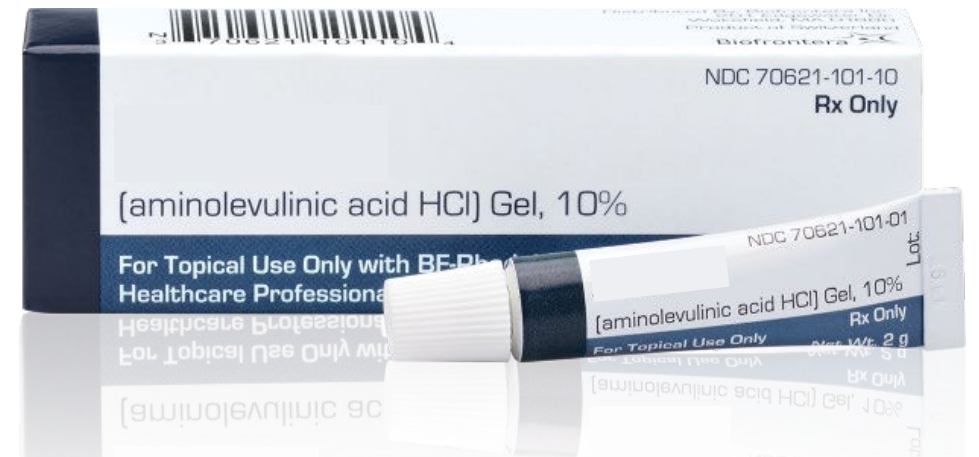


**J7308**

## 10% ALA Nanoemulsion Gel

No mixing required, stable at room temperature for 24 months

Indicated for face and scalp



**J7345**

# FIELD THERAPY FOR AK: A STRUCTURED REVIEW OF LITERATURE ON EFFICACY, COST, & ADHERENCE

**Number of treated AK** per 1000 Medicare patients **rose 14.6%** from 2007 to 2015. In 2013, **the estimated cost of treating AK in the US was \$1.68 billion.**

PubMed, Embase, Web of Science and Google Scholar **database searches from Oct 2020 to Mar 2021 for articles on AK field therapy.**

**Effective cost was calculated as total cost divided by Clearance Rate (CR),** to approximate the cost of achieving 100% CR in a single patient.

5-FU has a wide range of total cost from \$433 for 4% cream to \$1503 for 0.5% cream. **Total cost of PDT is \$540 for a single round using ALA 10% gel.**

**Field treatment with 5-FU and PDT have similar effective costs.**

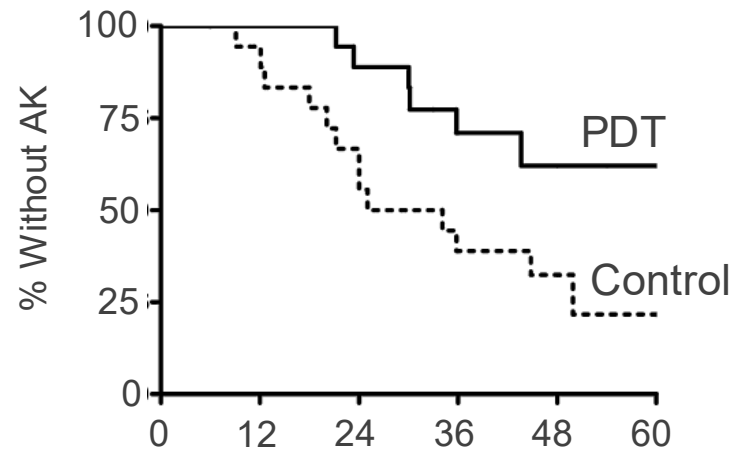
**Effect of adherence on real-world efficacy and long-term clearance favors shorter term topical regimens or in-office PDT procedures**

Product	Regimen	Cost (\$)			
		Regimen	CPT	Total	Effective
5-FU (4% cream) <sup>3</sup>	Daily x 4 wk	262.50	169.93	432.93	541.16–801.72
ALA (10% gel) <sup>2</sup>	1-2 session, 3 months apart	299.00	240.76	539.76	593.14–870.58
5-FU (5% cream) <sup>3</sup>	Twice daily x 4 wk	384.94*	169.93	554.93	737.90 – 956.77
Imiquimod (5% cream) <sup>4</sup>	2x/wk x 16 wk	529.80	169.93	699.93	1093.64 – 2916.38
Tirbanibulin (1% ointment) <sup>5</sup>	Daily x 5 days	990.00	169.93	1502.93	2148.02 – 2636.20
5-FU (0.5% cream) <sup>6</sup>	Daily x 4 wk	1332.08	169.93	1502.91	2589.67 – 4693.78
Diclofenac sodium (3% gel) <sup>7</sup>	Twice daily x 12 wk	943.57	169.93	1113.50	2715.85 – 5860.52
Imiquimod (3.75% cream) <sup>8</sup>	Daily x two 2-wk cycles 2 wk off	1040.93	169.93	1210.86	3363.50

# CLINICAL EVIDENCE: PDT AS EFFECTIVE FIELD TREATMENT

## Chemoprevention effect in organ transplant recipients

### PROBABILITY OF DEVELOPING AK<sup>1</sup>



#### Reduction in new AK incidence:

- Cyclic PDT (6 m intervals for 5 y)
- N = 25
- 16% MAL, 3h incubation, red light

### REDUCTION IN SCC INCIDENCE<sup>2</sup>

Assessment	SCC Lesion Count Median	Reduction from Baseline
1 yr before PDT	20	-----
1 yr after PDT	4	79%
2 yrs after PDT	1	95%

#### Reduction in SCC incidence vs. baseline:

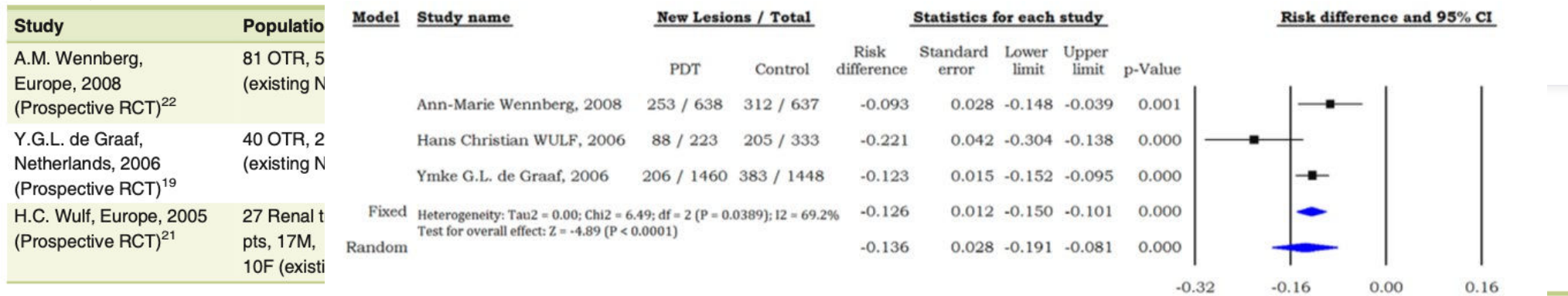
- Cyclic PDT (4-8 w intervals for 2 y)
- N = 12
- 20% ALA, 1h occluded incubation, blue light

1- Togsverd-Bo K, Omland SH, Wulf HC, et al. *Am J of Transplant.* 2015;15:2986-9.

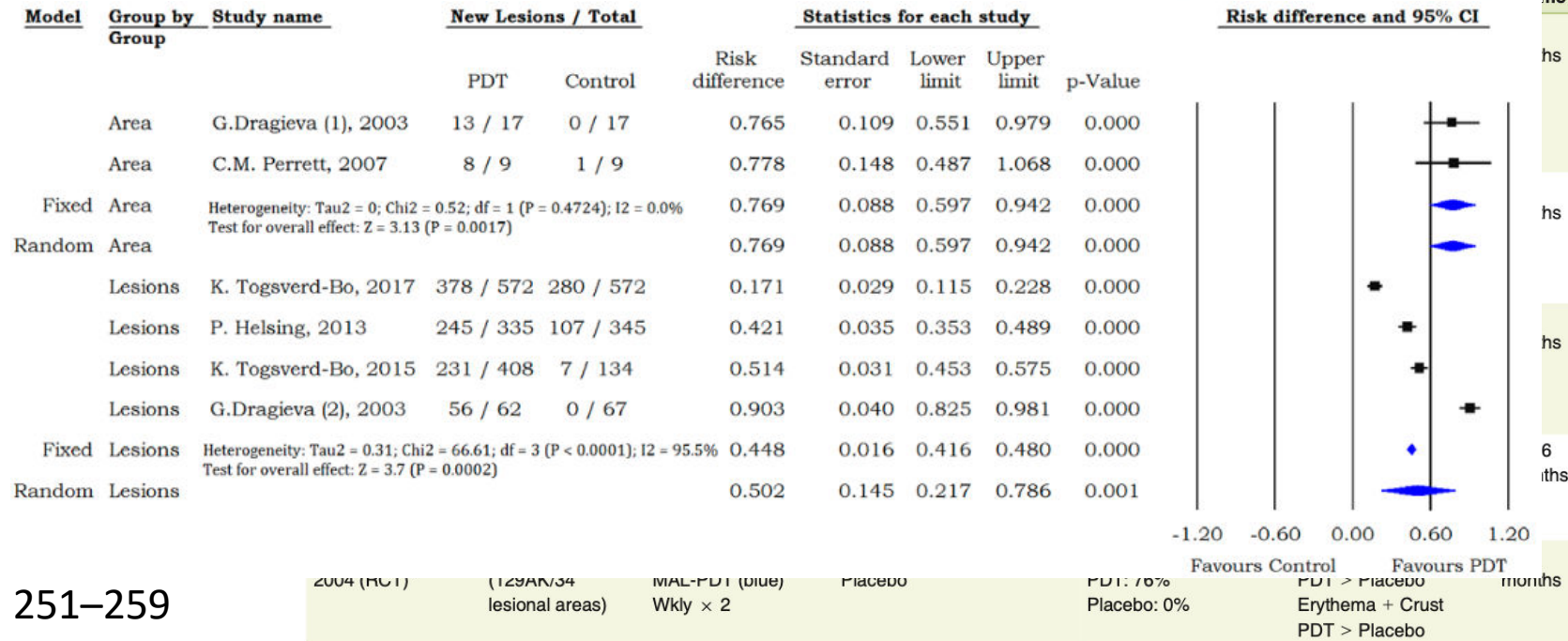
2- Adapted from: Willey A, Mehta S, Lee PK. *Dermatologic Surgery.* 2010;36:652-8.



# Chemoprevention in sOTR



Prevention



Treatment

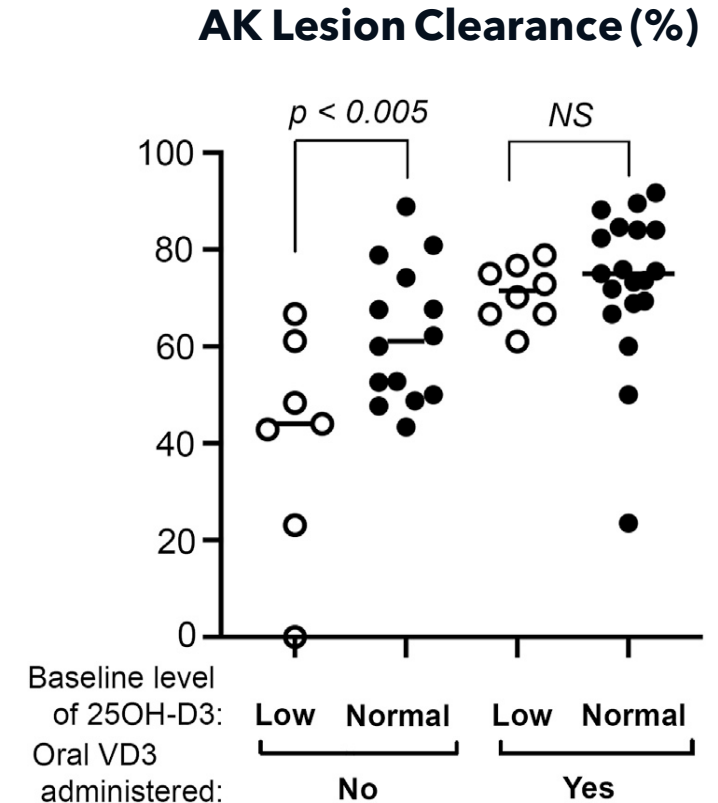
# IMPROVED PDT EFFICACY WITH VIT D PRE-TREATMENT

## Significant improvement of facial actinic keratoses after blue light photodynamic therapy with oral vitamin D pretreatment: An interventional cohort-controlled trial



Taylor A. Bullock, MD,<sup>a</sup> Jeffrey Negrey, BA, MA,<sup>b</sup> Bo Hu, PhD,<sup>c</sup> Christine B. Warren, MD, MS,<sup>a,d</sup>  
Tayyaba Hasan, PhD,<sup>e</sup> and Edward V. Maytin, MD, PhD<sup>a,b,d,e</sup>  
*Cleveland, Ohio and Boston, Massachusetts*

- **n=58, oral Vit. D for 5-14 days prior to PDT session**
- **PDT Protocol:** 15 minutes incubation, 30 min illumination with blue light (20 J/cm<sup>2</sup>)
- **Endpoints:** AK lesion clearance (%) at 3 and 6 months
- **Results:** High-dose Vit. D<sub>3</sub> supplementation significantly improved overall AK lesion response (72.5% ± 13.6%) compared to without (54.4% ± 22.8%)





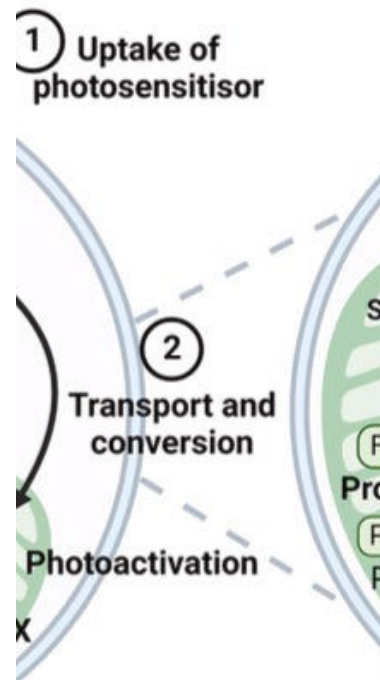
**Table 2**

Overview of the mechanisms of action of the included pretreatment compounds and their effects in combination with PDT.

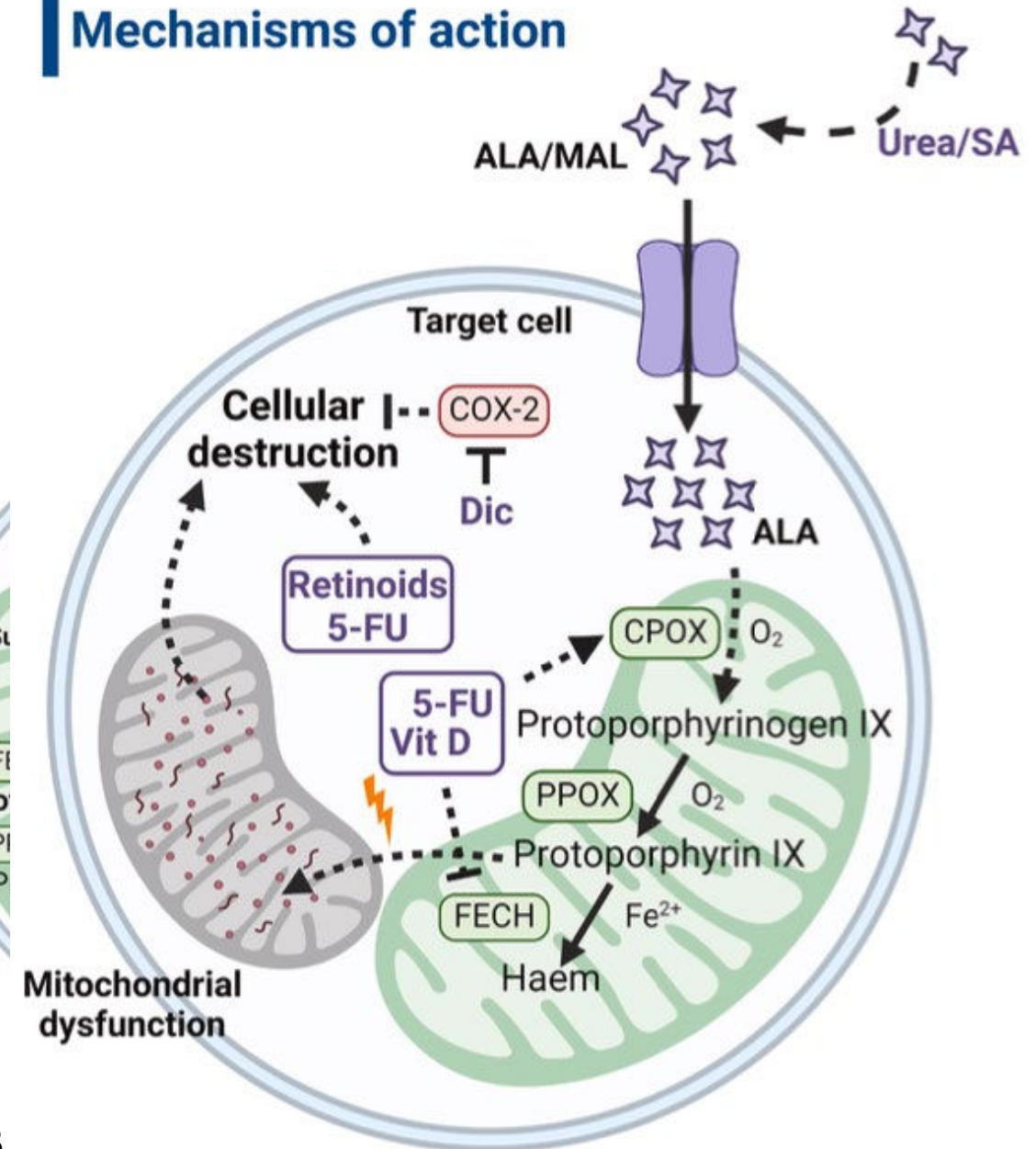
Compound	Mechanism of action	Effect on PDT procedure?	Proposed effect in combination with PDT
Penetration enhancers	<ul style="list-style-type: none"> <li>Enhances skin penetration</li> </ul>	Yes	<ul style="list-style-type: none"> <li>Increases uptake of PS</li> <li>Increases accumulation of PpIX</li> <li>Greater effect of PDT</li> </ul>
Vitamin D	<ul style="list-style-type: none"> <li>Induces differentiation</li> <li>Reduces proliferation</li> </ul>	Yes	<ul style="list-style-type: none"> <li>Upregulates CPOX expression</li> <li>Downregulates FECH expression</li> <li>Increases accumulation of PpIX</li> <li>Stimulates TNF-<math>\alpha</math> mediated apoptosis</li> <li>Greater effect of PDT</li> </ul>
Diclofenac	<ul style="list-style-type: none"> <li>Inhibits COX-2 activity</li> <li>Reduces pro-inflammatory cytokines</li> <li>Inhibits angiogenesis</li> </ul>	No	<ul style="list-style-type: none"> <li>Inhibits COX-2-mediated survival</li> <li>Stimulates TNF-<math>\alpha</math> mediated apoptosis</li> <li>Overall clearance boosted by PDT and diclofenac</li> <li>Reduces associated inflammation</li> <li>Upregulates p53 expression</li> <li>Induces caspase proteins</li> <li>Overall clearance boosted by PDT and retinoids</li> </ul>
Retinoids	<ul style="list-style-type: none"> <li>Induces differentiation</li> <li>Reduces proliferation</li> </ul>	No	<ul style="list-style-type: none"> <li>Upregulates CPOX expression</li> <li>Downregulates FECH expression</li> <li>Increases accumulation of PpIX</li> <li>Greater effect of PDT</li> <li>Impairs DNA replication</li> <li>Overall clearance boosted by PDT and 5-FU</li> </ul>
5-fluorouracil	<ul style="list-style-type: none"> <li>Interferes with thymidylate synthase</li> <li>Impair DNA replication</li> <li>Induces apoptosis</li> </ul>	Yes	

Abbreviations: 5-FU: 5-fluorouracil, COX-2: cyclooxygenase 2, CPOX: coproporphyrinogen oxidase, FECH: ferrochelatase, PDT: photodynamic therapy, PpIX: protoporphyrin IX, PS: photosensitiser.

# Work?



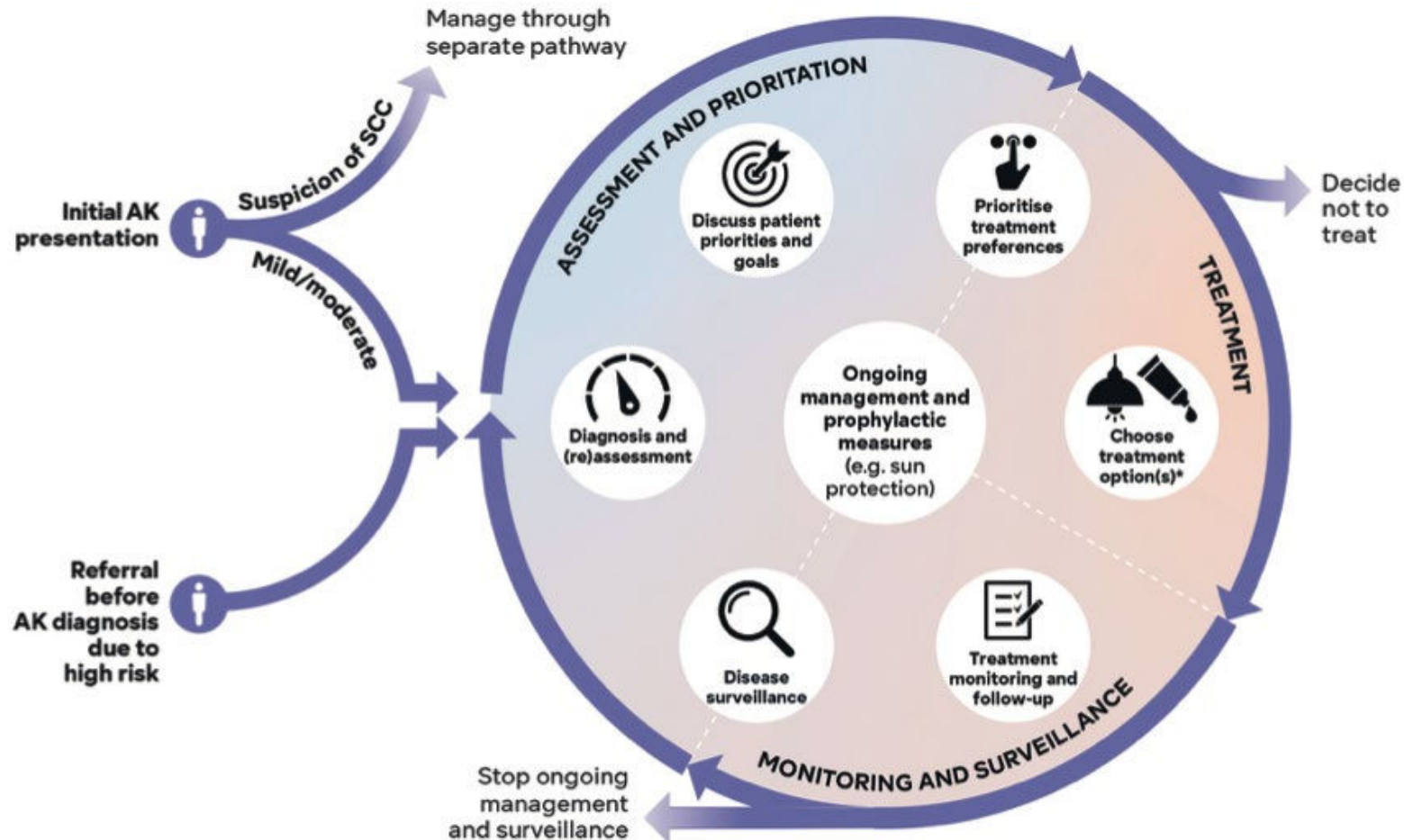
## Mechanisms of action



# Personalizing Actinic Keratosis Management

A

Red-light PDT with MAL 160 mJ/cm<sup>2</sup>  
5-FU 5% cream  
Natural daylight PDT with MAL 160 mJ/cm<sup>2</sup>  
Artificial daylight PDT with MAL 160 mJ/cm<sup>2</sup>  
Red-light PDT with ALA 78 mJ/cm<sup>2</sup>  
Natural daylight PDT with ALA 78 mJ/cm<sup>2</sup>  
Imiquimod 5% cream  
Cryotherapy  
5-FU in salicylic acid 10% lacquer  
Imiquimod 3.75% cream  
Tirbanibulin 10 mg/g ointment  
Diclofenac sodium 3% in HA gel



# "Painless PDT" Does it Work?

All Sites		Erythema Score		
Number of AK		Low	Moderate	High
0		75 (60.0%)	38 (30.4%)	12 (9.6%)
1-4		88 (33.6%)	123 (46.9%)	51 (19.5%)
5-10		12 (22.6%)	19 (35.9%)	22 (41.5%)
>10		3 (23.1%)	4 (30.8%)	6 (46.2%)

$p < 0.0001$

Forehead		Erythema Score		
Number of AK		Low	Moderate	High
0		8 (66.7%)	3 (25.0%)	1 (8.3%)
1-4		26 (43.3%)	26 (43.3%)	8 (13.3%)
5-10		4 (25.0%)	8 (50.0%)	4 (25.0%)
>10		2 (20.0%)	4 (40.0%)	4 (40.0%)

$p = 0.15$

Temples		Erythema Score		
Number of AK		Low	Moderate	High
0		15 (83.3%)	3 (16.7%)	0 (0.0%)
1-4		25 (41.0%)	27 (44.3%)	9 (14.8%)
5-10		3 (21.4%)	6 (42.9%)	5 (35.7%)
>10		1 (50.0%)	0 (0.0%)	1 (50.0%)

$p = 0.002$

Cheeks		Erythema Score		
Number of AK		Low	Moderate	High
0		1 (6.7%)	11 (73.3%)	3 (20.0%)
1-4		9 (16.1%)	29 (51.8%)	18 (32.1%)
5-10		5 (23.8%)	5 (23.8%)	11 (52.4%)
>10		0 (0.0%)	0 (0.0%)	1 (100.0%)

$p = 0.06$

Nose		Erythema Score		
Number of AK		Low	Moderate	High
0		12 (32.4%)	17 (45.9%)	8 (21.6%)
1-4		9 (16.4%)	31 (56.4%)	15 (27.3%)
5-10		0 (0.0%)	0 (0.0%)	2 (100.0%)

$p = 0.09$

Supralabial		Erythema Score		
Number of AK		Low	Moderate	High
0		39 (90.7%)	4 (9.3%)	0 (0.0%)
1-4		19 (63.3%)	10 (33.3%)	1 (3.3%)

$p = 0.009$



# What About Indoor Daylight PDT?

**a**

**h**

**c**

Timepoint	Site	Red-lamp treatment	Indoor-daylight treatment
Pre-treatment lesions (mean $\pm$ SD)	Face	6 $\pm$ 2	7 $\pm$ 3
	Forehead	6 $\pm$ 3	6 $\pm$ 4
	Scalp	10 $\pm$ 7	13 $\pm$ 5
1-month post-treatment clearance rate (mean $\pm$ SD)	Face	60 $\pm$ 15%	65 $\pm$ 22%
	Forehead	59 $\pm$ 23%	70 $\pm$ 20%
	Scalp	49 $\pm$ 33%	46 $\pm$ 32%
6-month post-treatment clearance rate (mean $\pm$ SD)	Face	69 $\pm$ 35%	72 $\pm$ 16%
	Forehead	65 $\pm$ 28%	73 $\pm$ 31%
	Scalp	60 $\pm$ 39%	59 $\pm$ 26%

400 450 500 550 600 650 700 750  
Wavelength (nm)

400 450 500 550 600 650 700 750  
Wavelength (nm)

400 450 500 550 600 650 700 750  
Wavelength (nm)

# SEASONAL & GEOGRAPHICAL TRENDS IN PDT & CRYOSURGERY UTILIZATION IN THE US: A CROSS-SECTIONAL STUDY (2015-2022)

## RESULTS:

PDT procedural claims are:

- Affected by season, significantly increasing in the cooler months (Sep-Feb) and decreasing in warmer months (Mar-Aug) ( $P=0.0000159$ )
- Correlated by geographic location

States with larger seasonal changes have a larger change in PDT claims between cooler and warmer months.

Database of aggregate of closed and open medical claims (CPT & HCPCS) from a broad selection of commercial payers and CMS.



7.91 million patient records extracted through CPT codes from 50 states and 4 territories between 2015 – 2022.

Cryosurgery

CPT codes 17000, 17003 & 17004

PDT

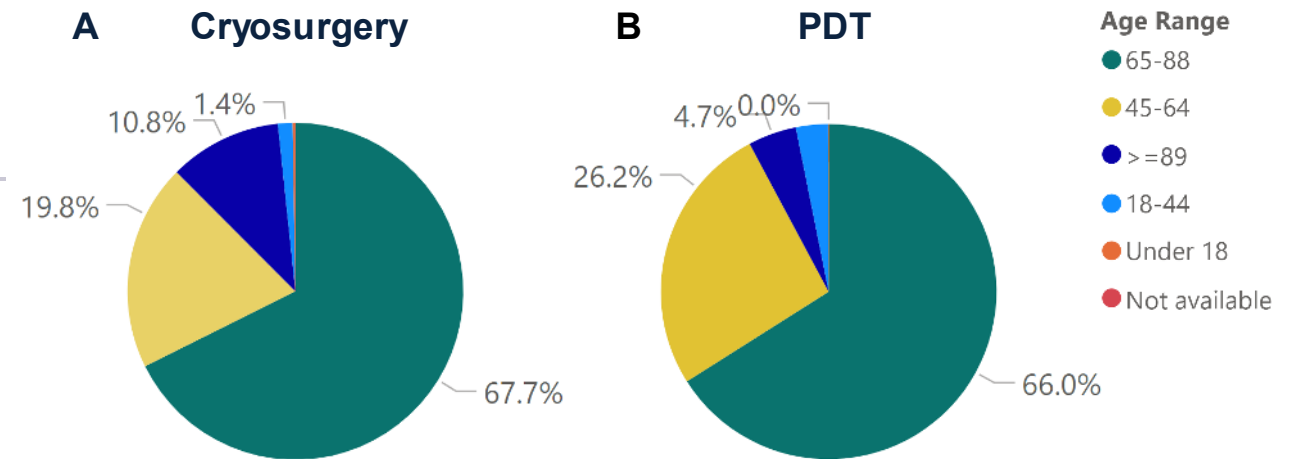
CPT codes 96567, 96573 and 96574



Stratified using location & meteorologically defined seasons<sup>4</sup>

Winter: Dec 1 – Feb 28; Spring: Mar 1 – May 31,  
Summer: Jun 1 – Aug 31; Fall: Sep 1 – Nov 30

## Majority of patients were between ages 65-88 for both PDT and cryo

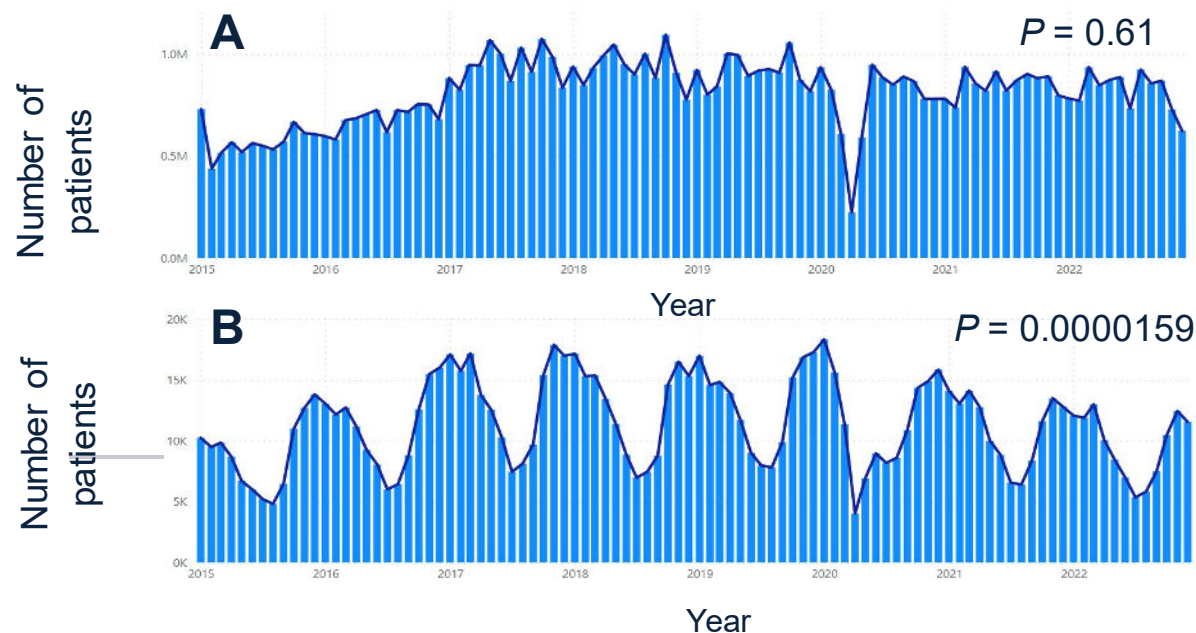


**Figure 1.** Patients stratified by age for cryosurgery and PDT between 2015-2022.



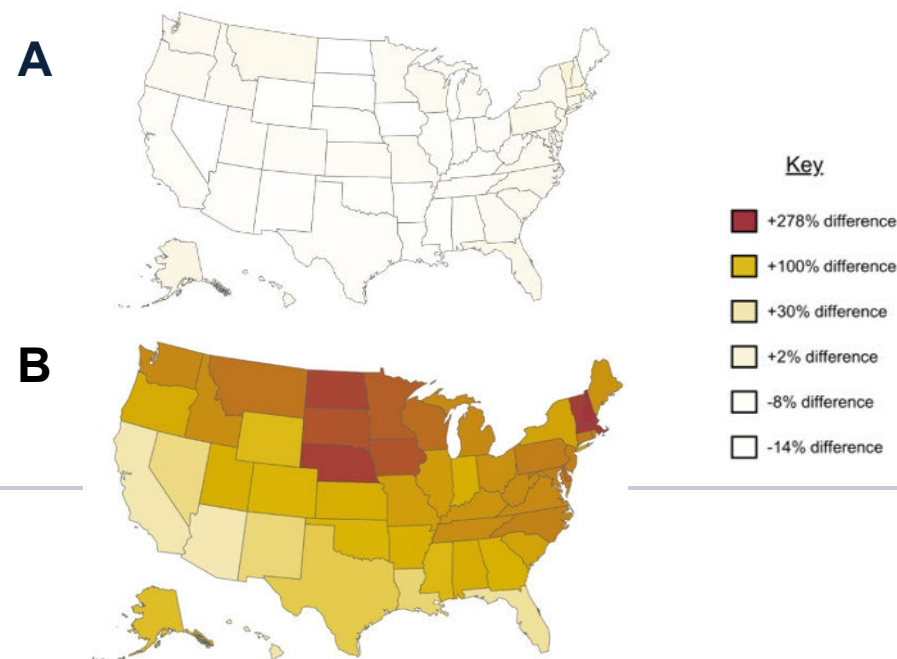
# SEASONAL & GEOGRAPHICAL TRENDS IN PDT & CRYOSURGERY UTILIZATION IN THE US: A CROSS-SECTIONAL STUDY (2015-2022)

PDT procedural claims show seasonality, peaking during cooler months and decreasing during the warmer months, while cryosurgery procedural claims remain relatively stable year-round



**Figure 2.** Number of (a) cryosurgery procedural claims and (b) PDT procedural claims in the US by month between 2015-2022. *P*-values were calculated through sinusoidal regression and data from 2020 was excluded from the analysis due to the COVID-19 pandemic.

Difference between PDT procedural claims in the winter (Dec-Feb) and summer months (Jun-Aug) varies by geographic location



**Figure 3.** Percentage difference in (a) cryosurgery procedural claims and (b) PDT procedural claims in the winter months vs. summer months stratified by geographic location.

## Top 15 states according to cryosurgery and PDT procedural claims

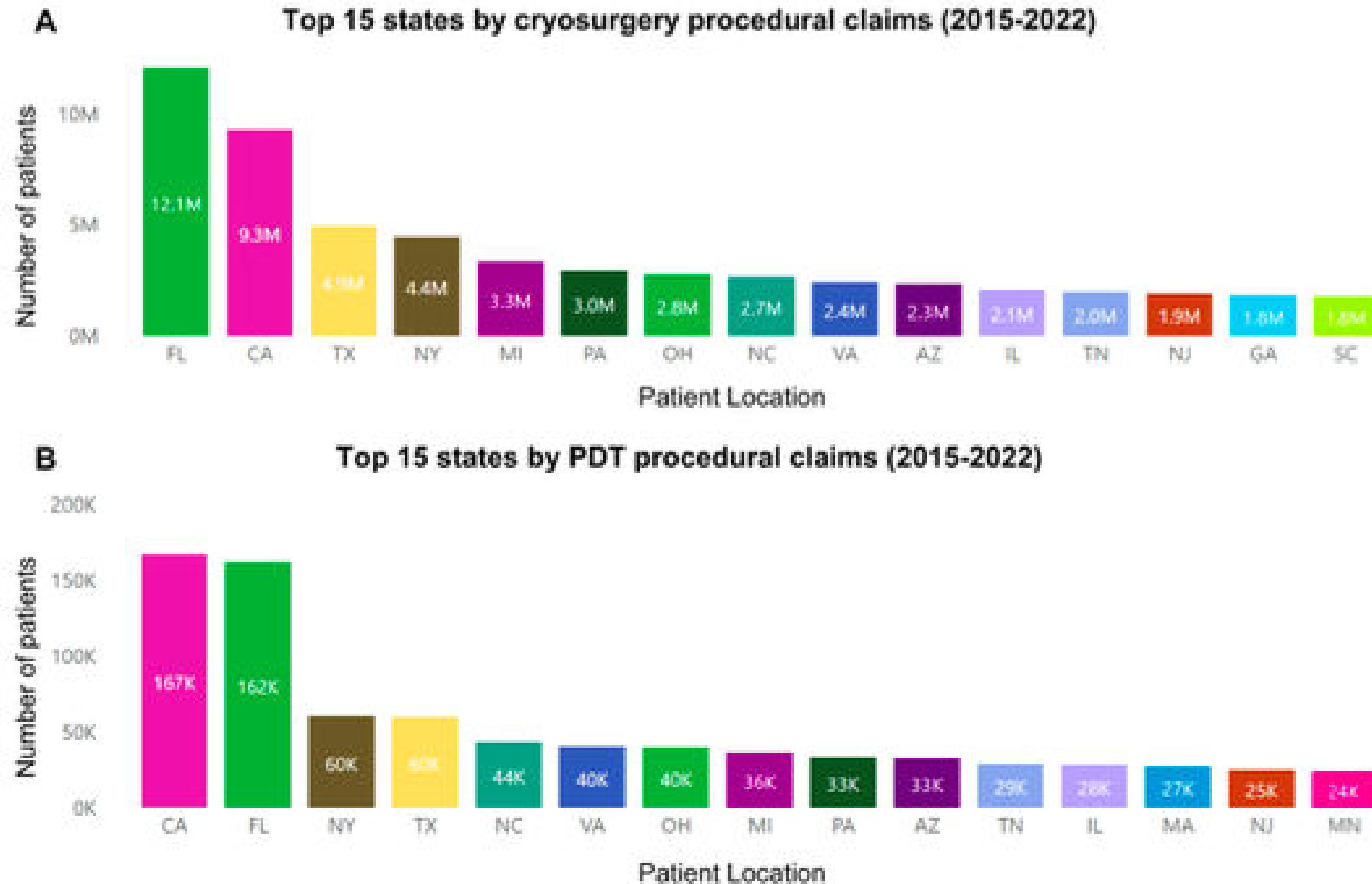


Figure 2. Top 15 states by (a) cryosurgery and (b) PDT procedural claims between 2015-2022.

# What Am I Doing In Clinic?

- Usually starting with cryosurgery
- Using tirbanibulin for small field pattern AK
- Then doing PDT for larger field AK, face, scalp, extremities, at least 2 treatments and cycling depending on disease burden
- Adding in 5-FU 5%/calcipotriene or 4% 5-FU for larger field mixed sometimes with imiquimod

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