

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
<b>How common is the problem?</b>	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
<b>Is this diagnostic or monitoring test accurate?</b> (Diagnosis)	Systematic review of cross-sectional studies with consistently applied reference standard and blinding	Individual cross-sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
<b>What will happen if we do not add a therapy?</b> (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor-quality prognostic cohort study**	n/a
<b>Does this intervention help?</b> (Treatment Benefits)	Systematic review of randomized trials or <i>n</i> -of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
<b>What are the COMMON harms?</b> (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, <i>n</i> -of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
<b>What are the RARE harms?</b> (Treatment Harms)	Systematic review of randomized trials or <i>n</i> -of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
<b>Is this (early detection) test worthwhile?</b> (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

\* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size. \*\* As always, a systematic review is generally better than an individual study.

**Table 2.** Review of efficacy and tolerability of actinic keratosis treatments

Topical agent	Regimen	Localization	Local intervention (L) or field cancerisation treatment (F)	Maximum treatable area	Efficacy	Ranking of long-term patient/lesion-specific clearance rates ranking based on network meta-analysis (RR 95% CI) *	Provisional grading of application site reactions**	Systemic side-effects	Ranking of efficacy based on network meta-analysis (OR, 95% CI) ***
5% 5-FU	twice daily 4 weeks	face, scalp neck, extremities	F	500 cm <sup>2</sup>	47-94% lesions 38-96% patients	2.80 (0.99-7.86) patient 1.59 (0.82-3.09) lesion	+++	rarely myelosuppression	35.0 (10,2-164.4)
0.5% 5-FU+10 salicylic acid%	once daily 4 weeks	face, scalp neck, extremities	F+L	25 cm <sup>2</sup>	39.4%-98.7% lesions 55.4% patients	NA (patient) 0.92 (0.44- 1.93) lesion	++	none	7.6 (4.6-13.5)
4% 5-FU	once daily 4 weeks	face and scalp	F	none	80.5% patients	NA (patient) NA (lesion)	+++ (better than 5% 5FU)	rarely myelosuppression	30.3 (9.1-144.7)
5% imiquimod	3 times a week 4 weeks, for residual lesion another 4 weeks	face and scalp	F	1 sachet per day	45.1%-93.6% lesions 24%-85% patients	5.98, 2.26-15.84 patient 2.83 (1.00-8.02) lesion	++	rarely flu-like symptoms	17.9 (9.1-36.6)
3.75% imiquimod	once daily 2 weeks, 2 weeks break, than again once daily 2 weeks	face and scalp	F	none	34%-81.8% lesions	0.80 (0.18-3.51) patient NA (lesion)	++	rarely flu-like symptoms	8.5 (3.5-22.4)
1% tirbanibulin	once daily 5 days	face and scalp	F	25 cm <sup>2</sup>	44%-54% lesions 76%-82% patients	NA (patient) NA (lesion)	+	none	11.1% (6.2-20.9)
3% diclofenac	Twice daily 60-90 days	face and scalp	F	200 cm <sup>2</sup> or 8 g/d	51.8%-81% lesions 27%-50% patients	1.13 (0.13-9.89) 0.75 (0.38-1.46)	+	none	2.9 (1.9-4.3)

\*adapted from Steeb et al.(140); \*\*adapted from Koch et al. (125); \*\*\* adapted from Heppt el al. (123)

**Figure 1:** Treatment algorithm for actinic keratoses

