Supplementary Online Content

Massey PR, Schmults CD, Li SJ, et al. Consensus-based recommendations on the prevention of squamous cell carcinoma in solid organ transplant recipients: a Delphi consensus statement. *JAMA Dermatol.* Published online September 1, 2021. doi:10.1001/jamadermatol.2021.3180

eAppendix. Administered Surveys

This supplementary material has been provided by the authors to give readers additional information about their work.

Delphi Round 1

ITSCC Proposed Stages

Stage 1. No actinic keratosis (AK) - photodamage only (lentigines, poikiloderma, rhytides)
Stage 2. Discrete AK
Stage 3. Diffuse AK +/- Squamous cell carcinoma in situ (SCCis) in a given field
Stage 4. First invasive cutaneous squamous cell carcinoma (cSCC)
Stage 5. Multiple invasive cSCCs
Stage 6. High-risk cSCC (20% risk of nodal metastasis)

Stage-specific questions

There are multiple ways of addressing medical management for prevention of skin cancer in solid organ transplant recipients (SOTR). For the following questions, please select options you would consider most acceptable in medical management. Please consider a typical immunosuppressed solid organ transplant recipient you would see in your clinic.

Part 1: Demographics

Fields for:

a. Name
b. Email
c. Country
d. Practice
e. Surgeon, yes or no
f. Years in practice

Part 2: Sunscreen and skin surveillance

1. Do you routinely recommend skin surveillance to all SOTRs? If no, please explain why.

2. Do you routinely recommend sunscreen to all SOTRs? If no, please explain why.

Part 3: Stage-based questions

Stage 1

3. Which of the following do you consider to be an acceptable medical management option for prevention of skin cancer in a SOTR who presents with Stage 1 actinic damage (photo damage only, exemplified by lentigines, poikiloderma and rhytides, without actinic keratosis)?

Check all that apply:

a. Observation only *(if selected no further choices available)*
b. Cryotherapy
c. Curettage
d. Topical 5-FU
e. Topical 5-FU and calcipotriene
f. Topical 5-FU-based chemowraps
g. Topical Imiquimod
h. Topical Diclofenac
i. Topical Ingenol Metabutate
j. Red Light PDT
k. Blue Light PDT
l. Daylight PDT
m. Ablative fractional laser-based PDT
n. Oral Nicotinamide
o. Oral Acitretin
p. Other: (please list other modalities, separated with a comma)

<u>Stage 2</u>

4. Which of the following do you consider to be an acceptable medical management option for prevention of skin cancer in a SOTR who presents with Stage 2 disease (discrete actinic keratosis only)?

Check all that apply:

a. Observation only *(if selected no further choices available)*
b. Cryotherapy
c. Curettage
d. Topical 5-FU
e. Topical 5-FU and calcipotriene
f. Topical 5-FU-based chemowraps
g. Topical Imiquimod
h. Topical Diclofenac
i. Topical Ingenol Metabutate
j. Red Light PDT
k. Blue Light PDT
l. Daylight PDT
m. Ablative fractional laser-based PDT
n. Oral Nicotinamide
o. Oral Acitretin
p. Other: (please list other modalities, separated with a comma)

5. Of the options selected which you would consider most acceptable, please rank your top 3:

Stage 3

6. Which of the following do you consider to be an acceptable medical management option for prevention of skin cancer in a SOTR who presents with Stage 3 disease (diffuse actinic keratosis, with or without lesions concerning for in situ carcinoma)?

Check all that apply:

a. Cryotherapy
b. Curettage
c. Topical 5-FU
d. Topical 5-FU and calcipotriene
e. Topical 5-FU-based chemowraps
f. Topical Imiquimod
g. Topical Diclofenac
h. Topical Ingenol Metabutate
i. Red Light PDT
j. Blue Light PDT
k. Daylight PDT
l. Ablative fractional laser-based PDT
m. Oral Nicotinamide
n. Oral Acitretin
o. Other: (please list other modalities, separated with a comma)

7. Of the options selected which you would consider most acceptable, please rank your top 3:

Stage 4

8. Which of the following do you consider to be an acceptable medical management option for prevention of skin cancer in a SOTR who presents with Stage 4 disease (first invasive cutaneous squamous cell carcinoma) in a given field? Please assume the lesion has been surgically treated with negative margins.

Check all that apply:

a. Oral Nicotinamide
b. Oral Acitretin
c. Oral Capecitabine
d. Consideration of switch to mTOR inhibition
e. Consideration of reduction of immunosuppression
f. Other: (please list other modalities, separated with a comma)

9. Of the options selected which you would consider most acceptable, please rank your top 3:

Stage 5

10. Which of the following do you consider to be acceptable for medical management of a SOTR who presents with Stage 5 disease (multiple invasive cutaneous squamous cell carcinomas) in a given field, assuming the lesions **have been** appropriately removed surgically?

Check all that apply:

a. Oral Nicotinamide
b. Oral Acitretin
c. Oral Capecitabine
d. Consideration of switch to mTOR inhibition
e. Consideration of reduction of immunosuppression
f. Other: (please list other modalities, separated with a comma)

11. Of the options selected which you would consider most acceptable, please rank your top 3:

Stage 6: (Note: for questions 12 and 13 we are interested in dermatological medical management only. Any techniques involving incising the dermis, radiation, imaging, SLNB, chemotherapy, immunotherapy are beyond the scope of this question)

12. Which of the following do you consider to be acceptable for medical management of a SOTR with Stage 6 disease (high-risk cutaneous squamous cell carcinoma with at least a 20% risk of nodal metastasis), assuming the lesion is treated surgically with negative margins?

Check all that apply:

a. Oral Nicotinamide
b. Oral Acitretin
c. Oral Capecitabine
d. Consideration of switch to mTOR inhibition
e. Consideration of reduction of immunosuppression
f. Other: (please list other modalities, separated with a comma)

13. Of the options selected which you would consider most acceptable, please rank your top 3:

Part 4: Treatment-based questions

14. When is the ideal time to begin topical field therapy (e.g., topical 5-FU, imiquimod, Red/Blue light PDT) in a SOTR?
    a. Photodamaged skin in a given field
    b. Development of 1st actinic keratosis in a given field
    c. Development of multiple actinic keratoses in a given field
    d. Development of diffuse actinic keratoses, with or without lesions concerning for in situ carcinoma in a given field

e. Development of squamous cell carcinoma in situ in a given field
f. Development of 1st invasive SCC in a given field
g. Rate of formation-based strategy (e.g., upon formation of ___ actinic keratoses in ____ years) in a given field
h. I utilize some other threshold (Please explain)

15. When is the ideal time to begin oral nicotinamide in a SOTR for skin cancer prevention (check all that apply)?
    a. Photodamaged skin in a given field
    b. Development of 1st AK
    c. Field cancerization
    d. Development of 1st invasive SCC
    e. Development of >1 invasive SCC
    f. Development of 1st high risk SCC
    g. Rate of formation-based strategy (e.g., upon formation of ___ SCC in 1 year)
    h. I utilize some other threshold (Please explain)

16. When is the ideal time to begin oral acitretin in a SOTR for skin cancer prevention (check all that apply)?
    a. Photodamaged skin in a given field
    b. Development of 1st AK
    c. Presence of field cancerization
    d. Development of 1st invasive SCC
    e. Development of >1 invasive SCC
    f. Development of 1st high risk SCC
    g. Rate of formation-based strategy (e.g., upon formation of ___ SCC in 1 year)
    h. I utilize some other threshold (Please explain)

17. When is the ideal time to begin oral capecitabine in a SOTR for skin cancer prevention (check all that apply)?
    a. Development of 1st AK
    b. Presence of field cancerization
    c. Development of 1st invasive SCC
    d. Development of >1 invasive SCC
    e. Development of 1st high risk SCC
    f. Rate of formation-based strategy (e.g., upon formation of ___ SCC in 1 year)
    g. I utilize some other threshold (Please explain)

18. When is the ideal time to consider reduction of immunosuppression in a SOTR for skin cancer prevention (check all that apply)?
    a. Presence of field cancerization
    b. Development of 1st invasive SCC
    c. Development of >1 invasive SCC
    d. Development of 1st high risk SCC
    e. Rate of formation-based strategy (e.g., upon formation of ___ SCC in 1 year)
    f. I utilize some other threshold (Please explain)

19. When is the ideal time to consider switching to a mTOR-based immunosuppression in a SOTR for skin cancer prevention?
    a. Presence of field cancerization
    b. Development of 1st invasive SCC
    c. Development of >1 invasive SCC
    d. Development of 1st high risk SCC
    e. Rate of formation-based strategy (e.g., upon formation of ___ skin cancers in 1 year)
    f. I utilize some other threshold (Please explain)

20. **Please write any other considerations you might have regarding treatment options for medical management of skin cancer prevention in SOTR:**

Delphi Round 2

ITSCC Proposed cSCC Stages

Stage 1. No actinic keratosis (AK) - photodamage only (lentigines, poikiloderma, rhytides)
Stage 2. Discrete AK
Stage 3. Diffuse AK +/- Squamous cell carcinoma in situ (SCCis) in a given field
Stage 4. First invasive cutaneous squamous cell carcinoma (cSCC)
Stage 5. Multiple invasive cSCCs
Stage 6. High-risk cSCC (20% risk of nodal metastasis)

Part 1: Stage and scenario-specific questions

There are multiple management options for the prevention of skin cancer in solid organ transplant recipients (SOTR). For each clinical scenario below, please select options you would recommend/use.

Please answer each question independently of your answer to previous questions (e.g., if you have selected a treatment modality in a prior question, you may select that modality again in a subsequent question).

Please assume that in each instance, the presenting patient is a 50-year-old with a solid organ transplant on immunosuppression and that you have access to each treatment modality listed.

1.For Stage 1 actinic damage (**photodamage only, exemplified by lentigines, poikiloderma, and rhytids, without actinic keratosis**), which of the following medical management options for the prevention of skin cancer **do you use in such a case?**

(You may choose more than 1 option)

a. Preventative measures as defined by education, sun protection strategies, sunscreen, and/or skin surveillance
b. Topical 5-FU-based modality (monotherapy or in combination with another treatment modality with the intent to augment the effect of 5-FU)
c. PDT (Red or blue light, in office or daylight)
d. Oral Nicotinamide
e. Other: (please state)

Stage 2

2.For Stage 2 disease (discrete actinic keratosis only), evidenced by **4-5 total thin, gritty actinic keratoses that are better felt than seen**, **scattered in the same anatomic area but which <u>are not</u> in close proximity to one another,** which of the following medical management options for the prevention of skin cancer **do you use in such a case?**

Pick one option:

a. Observation only
b. Lesion-directed therapy only
c. Field therapy only
d. Lesion directed therapy followed by field therapy

e. Other (please state)

2a - 1– if option “a” or “e” is selected, no further questions.

2a - 2 - (Branching logic) - if option “b” is selected: Which lesion-directed therapy **do you use in such a case?**

Pick as many options as needed:

a. Lesion-directed cryotherapy
b. Lesion-directed removal of hyperkeratosis by mechanical means (e.g., sharp removal, curettage)
c. Lesion-directed topical 5-FU
d. Lesion-directed topical 5-FU in combination with another topical modality to augment the effect of 5-FU (e.g., topical retinoid, calcipotriene)
e. Lesion-directed topical Imiquimod
f. Lesion-directed PDT (Red or blue light, in office or daylight)
g. Other: (please state)

2a -3. (Branching logic)- if option “c” is selected: Which field therapy **do you use in such a case?**

Pick one option:

a. Field topical 5-FU
b. Field topical 5-FU in combination with another topical modality to augment the effect of 5-FU (e.g., topical retinoid, calcipotriene)
c. Field topical Imiquimod
d. Field PDT (Red or blue light, in office or daylight)
e. Other: (please state)

2a -4. (Branching logic) - if option “d” is selected, please route respondent to 2a-2 and 2a-3

2b. Would you start an oral chemopreventative agent in such a case? Yes/No

2b-1. (Branching logic) If yes, which oral chemopreventative medication **do you use in such a case?**

Pick as many options as needed. For example, if you would recommend both nicotinamide and acitretin select both a and b.

a. Oral nicotinamide
b. Oral Acitretin
c. Other (please state)

3.For Stage 2 disease (discrete actinic keratosis only), evidenced by **4-5 total thin, gritty actinic keratoses that are better felt than seen**, **scattered in the same anatomic area but which are in close proximity to one another,** which of the following medical management options for the prevention of skin cancer **do you use in such a case?**

Pick one option:

a. Observation only
b. Lesion-directed therapy only
c. Field therapy only
d. Lesion directed therapy followed by field therapy

d. Other (please state)

3a - 1– if option “a” or “e” is selected, no further questions.

3a - 2 - (Branching logic) - if option “b” is selected: Which lesion-directed therapy **do you use in such a case?**

Pick as many options as needed:

a. Lesion-directed cryotherapy
b. Lesion-directed removal of hyperkeratosis by mechanical means (e.g., sharp removal, curettage)
c. Lesion-directed topical 5-FU
d. Lesion-directed topical 5-FU in combination with another topical modality to augment the effect of 5-FU (e.g., topical retinoid, calcipotriene)
e. Lesion-directed topical Imiquimod
f. Lesion-directed PDT (Red or blue light, in office or daylight)
g. Other: (please state)

3a -3. (Branching logic)- if option “c” is selected: Which field therapy **do you use in such a case?**

Pick one option:

Pick one option:

a. Field topical 5-FU
b. Field topical 5-FU in combination with another topical modality to augment the effect of 5-FU (e.g., topical retinoid, calcipotriene)
c. Field topical Imiquimod
d. Field PDT (Red or blue light, in office or daylight)
e. Other: (please state)

3a -4. (Branching logic) - if option “d” is selected, please route respondent to 3a-2 and 3a-3

3b. Would you start an oral chemopreventative agent in such a case? Yes/No

3b-1. (Branching logic) If yes, which oral chemopreventative medication **do you use in such a case?**

Pick as many options as needed. For example, if you would recommend both nicotinamide and acitretin select both a and b.

a. Oral nicotinamide
b. Oral Acitretin
c. Other (please state)

4.For Stage 2 disease (discrete actinic keratosis only), evidenced by **4-5 total thick, hyperkeratotic actinic keratoses which can be both seen and felt**, **scattered in the same anatomic area but which are not in close proximity to one another,** which of the following medical management options for the prevention of skin cancer **do you use in such a case?**

Pick one option:

a. Observation only
b. Lesion-directed therapy only

c. Field therapy only
d. Lesion directed therapy followed by field therapy
e. (please state)

4a - 1– if option “a” or “e” is selected, no further questions.

4a - 2 - (Branching logic) - if option “b” is selected: Which lesion-directed therapy **do you use in such a case?**

Pick as many options as needed:

a. Lesion-directed cryotherapy
b. Lesion-directed removal of hyperkeratosis by mechanical means (e.g., sharp removal, curettage)
c. Lesion-directed topical 5-FU
d. Lesion-directed topical 5-FU in combination with another topical modality to augment the effect of 5-FU (e.g., topical retinoid, calcipotriene)
e. Lesion-directed topical Imiquimod
f. Lesion-directed PDT (Red or blue light, in office or daylight)
g. (please state)

4a -3. (Branching logic)- if option “c” is selected: Which field therapy **do you use in such a case?**

Pick one option:

a. Field topical 5-FU
b. Field topical 5-FU in combination with another topical modality to augment the effect of 5-FU (e.g., topical retinoid, calcipotriene)
c. Field topical Imiquimod
d. Field PDT (Red or blue light, in office or daylight)
e. Other (please state)

4a-4. (Branching logic) - if option “d” is selected, please route respondent to 4a-2 and 4a-3

4b. Would you start an oral chemopreventative agent **in such a case**? Yes/No

4b-1. (Branching logic) If yes, which oral chemopreventative medication **do you use in such a case?**

Pick as many options as needed. For example, if you would recommend both nicotinamide and acitretin select both a and b.

a. Oral nicotinamide
b.Oral Acitretin
c.Other (please state)

5.For Stage 2 disease (discrete actinic keratosis only), evidenced by **4-5 total thick, hyperkeratotic actinic keratoses which can be both seen and felt**, **scattered in the same anatomic area but which are in close proximity to one another,** which of the following medical management options for the prevention of skin cancer **do you use in such a case?**

Pick one option:

a.Observation only
b.Lesion-directed therapy only

c.Field therapy only
d.Lesion directed therapy followed by field therapy
e.Other (please state)

5a - 1– if option “a” or “e” is selected, no further questions.

5a - 2 - (Branching logic) - if option “b” is selected: Which lesion-directed therapy **do you use in such a case?**

Pick as many options as needed:

a. Lesion-directed cryotherapy
b. Lesion-directed removal of hyperkeratosis by mechanical means (e.g., sharp removal, curettage)
c. Lesion-directed topical 5-FU
d. Lesion-directed topical 5-FU in combination with another topical modality to augment the effect of 5-FU (e.g., topical retinoid, calcipotriene)
e. Lesion-directed topical Imiquimod
f. Lesion-directed PDT (Red or blue light, in office or daylight)
g. Other: (please state)

5a -3. (Branching logic)- if option “c” is selected: Which field therapy **do you use in such a case?**

Pick one option:

a. Field topical 5-FU
b. Field topical 5-FU in combination with another topical modality to augment the effect of 5-FU (e.g., topical retinoid, calcipotriene)
c. Field topical Imiquimod
d. Field PDT (Red or blue light, in office or daylight)
e. Other: (please state)

5a -4. (Branching logic) - if option “d” is selected, please route respondent to 5a-2 and 5a-3

5b. Would you start an oral chemopreventative agent **in such a case**? Yes/No

5b-1. (Branching logic) If yes, which oral chemopreventative medication **do you use in such a case?**

Pick as many options as needed. For example, if you would recommend both nicotinamide and acitretin select both a and b.

a. Oral nicotinamide
b. Oral Acitretin
c. Other (please state)

Stage 3

6. The patient presents with Stage 3 disease (diffuse actinic keratosis, with or without lesions concerning for in situ carcinoma).

6a. **Do you usually use field therapy in such a case?** Yes/no

6a-1. (Branching logic) If the answer to 5A is yes: which treatment for field therapy **do you usually use in such a case?**

Pick one option:

a. Field topical 5-FU
b. Field topical 5-FU in combination with another topical modality to augment the effect of 5-FU (e.g., topical retinoid, calcipotriene)
c. Field topical Imiquimod
d. Field PDT (Red or blue light, in office or daylight)
e. Other: (please state)

6a-2 (Branching logic) (for all patients who answer question 6A yes and complete 6a-1): would you recommend lesion-directed therapy to any hyperkeratotic lesions prior to initiation of field therapy **in such a case**? Yes/no

6a-3 (Branching logic) If the answer to 6A is no: would you recommend lesion-directed therapy to any hyperkeratotic lesions in such a case? Yes/No

6b. Would you start an oral chemopreventative agent once your (Stage 3-specific) therapy has been performed in such a case? Yes/No

6b-1. (Branching logic) If yes, which oral chemopreventative medication **do you use in such a case?**
Pick as many options as needed. For example, if you would recommend both nicotinamide and acitretin select both a and b.

a) Oral nicotinamide
b) Oral acitretin
c) Other (please state)

6c. For such patients, do you routinely speak with the transplant team regarding immunosuppression modification? Yes/no

6c-1. (Branching logic) If yes, which immunosuppression modification do you recommend in such a case?

Pick one option:

a) Reduction in immunosuppression dosing
b) Switch to mTOR inhibitor
c) I leave it up to the transplant team to decide
d) Other: (please state)

7.Consider a patient with Stage 4 disease – a recent diagnosis of his/her **first cutaneous SCC, a low-risk (AJCC 8th Edition T1/BWH T1) cutaneous SCC**. The remainder of the patient's cutaneous exam is within normal limits, including no evidence of actinic keratoses. The tumor has recently been appropriately cleared by surgery with negative margins. Which of the following medical management options for the prevention of further new skin cancers **do you usually use in such a case?**

Pick one option:

a. Observation only
b. Add oral chemoprevention (e.g. acitretin, nicotinamide) without making changes to immunosuppression

c. Speak with the transplant team regarding immunosuppression modification without adding oral chemoprevention
d. Add oral chemoprevention AND speak with the transplant team regarding immunosuppression modification
e. Other: (please state)

7a–1. if option “a” or “e” is selected, no further questions.

7a–2. (Branching logic) - if option “b” is selected: Which oral chemoprevention **do you usually use in such a case?**

Pick as many options as needed. For example, if you would recommend both nicotinamide and acitretin select both a and b.

a. Add oral nicotinamide
b. Add oral acitretin
c. Other (please state)

7a -3. (Branching logic)- if option “c” is selected: Which immunosuppression modification **do you usually recommend in such a case?**

Pick one option:

a. Reduction in immunosuppression dosing
b. Switch to mTOR inhibitor
c. I leave it up to the transplant team to decide
d. Other: (please state)

7a - 4. (Branching logic) - if option “d” is selected, please route respondent to 7a-2 and 7a-3

Stage 5

8. Consider a patient with Stage 5 disease (**multiple biopsy-proven invasive low risk cSCCs**): A review of her chart demonstrates a diagnosis of **5 low-risk (AJCC 8th Edition T1/BWH T1)** cutaneous SCC on the head and neck diagnosed **over the past 5 years**. The tumors have all been appropriately cleared by surgery with negative margins. Which of the following medical management options for the prevention of further new skin cancers **do you usually use in such a case?**

   Pick one option:

   a. Observation only
   b. Add oral chemoprevention (e.g. acitretin, nicotinamide) without making changes to immunosuppression
   c. Speak with the transplant team regarding immunosuppression modification without adding oral chemoprevention
   d. Add oral chemoprevention AND speak with the transplant team regarding immunosuppression modification
   e. Other: (please state)

8a-1 - if option “a” or “e” is selected, no further questions.

8a-2 - (Branching logic) - if option “b” is selected: Which oral chemoprevention **do you usually use in such a case?**

Pick as many options as needed. For example, if you would recommend both nicotinamide and acitretin select both a and b.

a. Add oral nicotinamide
b. Add oral acitretin
c. Add oral capecitabine
d. Other (please state)

8a-3. (Branching logic)- if option "c" is selected: Which immunosuppression modification **do you usually use in such a case?**

Pick one option:

a. Reduction in immunosuppression dosing
b. Switch to mTOR inhibitor
c. I leave it up to the transplant team to decide
d. Other: (please state)

8a-4. (Branching logic) - if option "d" is selected, please route respondent to 8a-2 and 8a-3

9. Consider a patient with Stage 5 disease (**multiple biopsy proven invasive low-risk cSCCs**): a review of her chart demonstrates a diagnosis **of 5 low-risk (AJCC 8th Ed T1/BWH T1) cSCCs** on the head and neck diagnosed **over the past 6 months**. The tumors have all been appropriately cleared by surgery with negative margins. Which of the following medical management options for the prevention of further new skin cancers **do you usually use in such a case?**

   Pick one option:

   a. Observation only
   b. Add oral chemoprevention (e.g. acitretin, nicotinamide) without making changes to immunosuppression
   c. Speak with the transplant team regarding immunosuppression modification without adding oral chemoprevention
   d. Add oral chemoprevention AND speak with the transplant team regarding immunosuppression modification
   e. Other: (please state)

9a-1 – if option "a" or "e" is selected, no further questions.

9a-2 - (Branching logic) - if option "b" is selected: Which oral chemoprevention **do you usually use in such a case?**

Pick as many options as needed. For example, if you would recommend both nicotinamide and acitretin select both a and b.

a. Add oral nicotinamide
b. Add oral acitretin
c. Add oral capecitabine
d. Other (please state)

9a-3. (Branching logic)- if option “c” is selected: Which immunosuppression modification **do you usually use in such a case?**

Pick one option:

a. Reduction in immunosuppression dosing
b. Switch to mTOR inhibitor
c. I leave it up to the transplant team to decide
d. Other: (please state)

9a-4. (Branching logic) - if option “d” is selected, please route respondent to 9a-2 and 9a-3

Stage 6

10.Consider a patient with **no prior history of NMSC** who presents with Stage 6 disease – a recent diagnosis of his/her **first cutaneous SCC** on the head and neck, which wa**s a high-risk (AJCC 8th Edition T3/BWH T2b) tumor**. The tumor has already been appropriately cleared by surgery with negative margins. The patient has photodamaged skin and a history of actinic keratoses, which have been effectively treated with cryotherapy. Which of the following medical management options for the prevention of further new skin cancers **do you usually use in such a case?**

Pick one option:

a.Observation only
b.Add oral chemoprevention (e.g. acitretin, nicotinamide) without making changes to immunosuppression
c.Speak with the transplant team regarding immunosuppression modification without adding oral chemoprevention
d.Add oral chemoprevention AND speak with the transplant team regarding immunosuppression modification
e.Other: (please state)

10a-1 – if option “a” or “e” is selected, no further questions.

10a-2 - (Branching logic) - if option “b” is selected: Which oral chemoprevention **do you usually use in such a case?**

Pick as many options as needed. For example, if you would recommend both nicotinamide and acitretin select both a and b.

a. Add oral nicotinamide
b. Add oral acitretin
c. Add oral capecitabine
d. Other (please state)

10a-3. (Branching logic)- if option “c” is selected: Which immunosuppression modification **do you usually use in such a case?**

Pick one option:

a. Reduction in immunosuppression dosing
b. Switch to mTOR inhibitor
c. I leave it up to the transplant team to decide

d. Other: (please state)

10a-4. (Branching logic) - if option "d" is selected, please route respondent to 10a-2 and 10a-3

11.Consider a patient with **5 low-risk (AJCC 8th Edition T1 or BWH T1) cutaneous SCC** on the head and neck diagnosed over the past **5 years** – who presents with a recent diagnosis of **a high-risk, AJCC 8th Edition T3/BWH T2b tumor** (Stage 6 disease). The tumor has already been appropriately cleared by surgery with negative margins. Which of the following medical management options for the prevention of further new skin cancers **do you usually use in such a case?**

Pick one option:

a.Observation only
b.Add oral chemoprevention (e.g. acitretin, nicotinamide) without making changes to immunosuppression
c.Speak with the transplant team regarding immunosuppression modification without adding oral chemoprevention
d.Add oral chemoprevention AND speak with the transplant team regarding immunosuppression modification
e.Other: (please state)

11a-1– if option "a" or "e" is selected, no further questions.

11a-2 – (Branching logic) – if option "b" is selected: Which oral chemoprevention **do you usually use in such a case?**

Pick as many options as needed. For example, if you would recommend both nicotinamide and acitretin select both a and b.

a. Add oral nicotinamide
b. Add oral acitretin
c. Add oral capecitabine
d. Other (please state)

11a-3. (Branching logic)- if option "c" is selected: Which immunosuppression modification **do you usually use in such a case?**

Pick one option:

a. Reduction in immunosuppression dosing
b. Switch to mTOR inhibitor
c. I leave it up to the transplant team to decide
d. Other: (please state)

11a-4. (Branching logic) – if option "d" is selected, please route respondent to 11a-2 and 11a-3

12. Consider a patient with Stage 5 disease - **5 low-risk (AJCC 8th Edition T1 or BWH T1) cutaneous SCC** on the head and neck diagnosed over the **past 6 months - and a recent diagnosis of a high-risk, AJCC 8th Edition T3/BWH T2b tumor**. The tumor has already been appropriately cleared by surgery with negative margins. Which of the following medical management options for the prevention of further new skin cancers **do you usually use in such a case?**

Pick one option:

a. Observation only
b. Add oral chemoprevention (e.g. acitretin, nicotinamide) without making changes to immunosuppression
c. Speak with the transplant team regarding immunosuppression modification without adding oral chemoprevention
d. Add oral chemoprevention AND speak with the transplant team regarding immunosuppression modification
e. Other: (please state)

12a-1 – if option “a” or “e” is selected, no further questions.

12a-2 - (Branching logic) - if option “b” is selected: Which oral chemoprevention **do you usually use in such a case?**

Pick as many options as needed. For example, if you would recommend both nicotinamide and acitretin select both a and b.

a. Add oral nicotinamide
b. Add oral acitretin
c. Add oral capecitabine
d. Other (please state)

12a-3. (Branching logic)- if option “c” is selected: Which immunosuppression modification **do you usually use in such a case?**

Pick one option:

a. Reduction in immunosuppression dosing
b. Switch to mTOR inhibitor
c. I leave it up to the transplant team to decide
d. Other: (please state)

12a-4. (Branching logic) - if option “d” is selected, please route respondent to 12a-2 and 12a-3

Part 2: Open ended and ranking questions

13.Open ended: Are there clinical scenarios where you think it’s more important to recommend mTOR conversion over reducing immunosuppression?

14.Ranking: In your opinion please rank the following immunosuppressants from most immunosuppressive to least immunosuppressive in terms of association with skin cancer formation in transplant patients.

Azathioprine
Mycophenolate mofetil
Calcineurin inhibitor
Prednisone
Sirolimus

Part 3: Questions about access to different treatment strategies

Please select “yes” or “no” as to whether you have access the following modalities in your practice:

15. Cryotherapy
    a. Yes
    b. No

16.Curettage
    a. Yes
    b. No

17.Topical 5-FU-based modalities
    c. Yes
    d. No

18.5-FU-based chemowraps
    a. Yes
    b. No

19.Topical imiquimod
    a. Yes
    b. No

20.Topical Diclofenac
    a. Yes
    b. No

21.In-office PDT
    a. Yes
    b. No

22.Daylight PDT
    a. Yes
    b. No

23.Oral nicotinamide
    a. Yes
    b. No

24.Oral acitretin
    a. Yes
    b. No

25.Oral capecitabine
    a. Yes
    b. No

26.Do you discuss alteration of immunosuppression of SOTR with transplant colleagues in your practice?
    a. Yes
    b. No

Round 3 Delphi Survey

ITSCC Proposed cSCC Stages

Stage 1. No actinic keratosis (AK) - photodamage only (lentigines, poikiloderma, rhytides)
Stage 2. Discrete AK
Stage 3. Diffuse AK +/- Squamous cell carcinoma in situ (SCCis) in a given field
Stage 4. First invasive cutaneous squamous cell carcinoma (cSCC)
Stage 5. Multiple invasive cSCCs
Stage 6. High-risk cSCC (20% risk of nodal metastasis)

Part 1: Stage-specific questions

1. In Round 2, we achieved consensus for the use of lesion-directed therapy utilizing cryotherapy for **thin** actinic keratoses **scattered** in the same anatomic area **but not in close proximity** to one another. Assume that you performed cryotherapy and the **patient now returns largely unchanged.** Which of the following medical management options for the prevention of skin cancer do you recommend?

Pick one option:

a. Observation only
b. Repeat lesion-directed therapy only
c. Field therapy only
d. Repeat lesion-directed therapy followed by field therapy
e. Other (please state)

1a - 1– if option “a” or “e” is selected, no further questions.

1a - 2 - (Branching logic) - if option “b” is selected: Which repeat lesion-directed therapy do you recommend in such a case?

Pick as many options as needed to capture your recommendation:

a. Lesion-directed cryotherapy
b. Lesion-directed removal of hyperkeratosis by mechanical means (e.g., sharp removal, curettage)
c. Lesion-directed topical 5-FU
d. Lesion-directed topical 5-FU in combination with another topical modality to augment the effect of 5-FU (e.g., topical retinoid, calcipotriene)
e. Lesion-directed topical Imiquimod
f. Lesion-directed PDT (Red or blue light, in office or daylight)
g. Other: (please state)

1a -3. (Branching logic)- if option “c” is selected: Which field therapy do you recommend in such a case?

Pick one option:

a. Field topical 5-FU
b. Field topical 5-FU in combination with another topical modality to augment the effect of 5-FU (e.g., topical retinoid, calcipotriene)
c. Field topical Imiquimod
d. Field PDT (Red or blue light, in office or daylight)
e. Other: (please state)

1a -4. (Branching logic) - if option “d” is selected, please route respondent to 1a-2 and 1a-3

2. Similarly, in Round 2 we achieved consensus for the use of lesion-directed therapy utilizing cryotherapy for **thick** actinic keratoses **scattered** in the same anatomic area **but not in close proximity** to one another. Assume that you performed cryotherapy and the **patient now returns largely unchanged.** Which of the following medical management options for the prevention of skin cancer do you recommend?
Pick one option:

a. Observation only
b. Repeat lesion-directed therapy only
c. Field therapy only
d. Repeat lesion-directed therapy followed by field therapy
e. Other (please state)

2a - 1– if option “a” or “e” is selected, no further questions.

2a - 2 - (Branching logic) - if option “b” is selected: Which repeat lesion-directed therapy do you recommend in such a case?

Pick as many options as needed to capture your recommendation:

a. Lesion-directed cryotherapy
b. Lesion-directed removal of hyperkeratosis by mechanical means (e.g., sharp removal, curettage)
c. Lesion-directed topical 5-FU
d. Lesion-directed topical 5-FU in combination with another topical modality to augment the effect of 5-FU (e.g., topical retinoid, calcipotriene)
e. Lesion-directed topical Imiquimod
f. Lesion-directed PDT (Red or blue light, in office or daylight)
g. Other: (please state)

2a -3. (Branching logic)- if option “c” is selected: Which field therapy do you recommend in such a case?

Pick one option:

a. Field topical 5-FU
b. Field topical 5-FU in combination with another topical modality to augment the effect of 5-FU (e.g., topical retinoid, calcipotriene)
c. Field topical Imiquimod
d. Field PDT (Red or blue light, in office or daylight)
e. Other: (please state)

2a -4. (Branching logic) - if option “d” is selected, please route respondent to 2a-2 and 2a-3

3. Now consider a new patient with **thin** actinic keratoses scattered in the **same anatomic area** but **which are clustered in close proximity** to one another. **No prior treatment has been undertaken.** Which of the following medical management options for the prevention of skin cancer do you recommend?

Pick one option:

a. Observation only
b. Lesion-directed therapy only
c. Field therapy only
d. Lesion directed therapy followed by field therapy
e. Other (please state)

3a - 1– if option “a” or “e” is selected, no further questions.

3a - 2 - (Branching logic) - if option “b” is selected: Which lesion-directed therapy do you use in such a case?

Pick as many options as needed to capture your recommendation:

a. Lesion-directed cryotherapy
b. Lesion-directed removal of hyperkeratosis by mechanical means (e.g., sharp removal, curettage)
c. Lesion-directed topical 5-FU
d. Lesion-directed topical 5-FU in combination with another topical modality to augment the effect of 5-FU (e.g., topical retinoid, calcipotriene)
e. Lesion-directed topical Imiquimod
f. Lesion-directed PDT (Red or blue light, in office or daylight)
g. Other: (please state)

3a -3. (Branching logic)- if option “c” is selected: Which field therapy do you use in such a case?

Pick one option:

a. Field topical 5-FU
b. Field topical 5-FU in combination with another topical modality to augment the effect of 5-FU (e.g., topical retinoid, calcipotriene)
c. Field topical Imiquimod
d. Field PDT (Red or blue light, in office or daylight)
e. Other: (please state)

3a -4. (Branching logic) - if option "d" is selected, please route respondent to 3a-2 and 3a-3

4. In Round 2, we achieved consensus for the use of lesion-directed therapy for thick actinic keratoses scattered in the **same anatomic area** but **which are clustered in close proximity to** one another. Assume you have chosen to perform lesion-directed therapy. Which **lesion-directed therapy modality** do you recommend?

Pick as many options as needed to capture your recommendation:

a. Lesion-directed cryotherapy
b. Lesion-directed removal of hyperkeratosis by mechanical means (e.g., sharp removal, curettage)
c. Lesion-directed topical 5-FU
d. Lesion-directed topical 5-FU in combination with another topical modality to augment the effect of 5-FU (e.g., topical retinoid, calcipotriene)
e. Lesion-directed topical Imiquimod
f. Lesion-directed PDT (Red or blue light, in office or daylight)
g. Other: (please state)

4b. Should field therapy be undertaken once your Stage 2-specific therapy has been performed in such a case? Yes/No

4b – 1. If yes, is selected: Which field therapy do you use in such a case?

Pick one option:

Pick one option:

a. Field topical 5-FU
b. Field topical 5-FU in combination with another topical modality to augment the effect of 5-FU (e.g., topical retinoid, calcipotriene)
c. Field topical Imiquimod
d. Field PDT (Red or blue light, in office or daylight)
e. Other: (please state)

4c. Would you **recommend** an oral chemopreventative agent once your Stage 2-specific therapy has been performed in such a case? Yes/No

5. For a patient with **field cancerized skin** in an anatomic area, you plan to **undertake lesion-directed therapy to any hyperkeratotic lesions followed by initiation of field therapy.** Which treatment for **field therapy** do you recommend?

Pick one option:

a. Field topical 5-FU, with or without another modality (e.g., curettage, topical retinoid, calcipotriene)
b. Field topical Imiquimod
c. Field PDT (Red or blue light, in office or daylight)
d. Other: (please state)

5b. Would you **recommend** an oral chemopreventative agent once your (Stage 3-specific) therapy has been performed in such a case? Yes/No

5b-1. (Branching logic) If yes, which oral chemopreventative medication **do you recommend in such a case?**

Pick as many options as needed to capture your recommendation. For example, if you would recommend both nicotinamide and acitretin select both a and b.

a) Oral nicotinamide
b) Oral acitretin
c) Other (please state)

[Please have participants "check through" this box prior to proceeding] Introductory stem to next section: For the next two questions (6 & 7), please consider the following scenario: The patient was recently diagnosed with his/her **first cutaneous SCC, a low-risk (AJCC 8th Edition T1/BWH T1) SCC**. The tumor has recently been appropriately cleared by surgery with negative margins.

6. Now consider that the patient is an **abdominal (liver, kidney and/or pancreas) transplant recipient.** Which of the following medical management options for the prevention of further new skin cancers do you recommend?

   Pick one option:

   a. Observation only
   b. Add oral chemoprevention (e.g. acitretin, nicotinamide) without making changes to immunosuppression
   c. Speak with the transplant team regarding immunosuppression modification without adding oral chemoprevention

d. Add oral chemoprevention AND speak with the transplant team regarding immunosuppression modification
e. Other: (please state)

6a–1. if option “a” or “e” is selected, no further questions.

6a–2. (Branching logic) - if option “b” is selected: Which oral chemoprevention do you recommend?

Pick as many options as needed. For example, if you would recommend both nicotinamide and acitretin select both a and b.

a. Add oral nicotinamide
b. Add oral acitretin
c. Other (please state)

6a -3. (Branching logic)- if option “c” is selected: Which immunosuppression modification do you recommend?

Pick one option:

a. Reduction in immunosuppression dosing
b. Switch to mTOR inhibitor
c. I leave it up to the transplant team to decide
d. Other: (please state)

6a - 4. (Branching logic) - if option “d” is selected, please route respondent to 6a-2 and 6a-3

7. Now consider that the patient is a **thoracic (lung and/or heart) transplant recipient.** Which of the following medical management options for the prevention of further new skin cancers do you recommend?

Pick one option:

a. Observation only
b. Add oral chemoprevention (e.g. acitretin, nicotinamide) without making changes to immunosuppression
c. Speak with the transplant team regarding immunosuppression modification without adding oral chemoprevention
d. Add oral chemoprevention AND speak with the transplant team regarding immunosuppression modification
e. Other: (please state)

7a–1. if option “a” or “e” is selected, no further questions.

7a–2. (Branching logic) - if option “b” is selected: Which oral chemoprevention do you recommend?

Pick as many options as needed to capture your recommendation. For example, if you would recommend both nicotinamide and acitretin select both a and b.

a. Add oral nicotinamide
b. Add oral acitretin
c. Other (please state)

7a -3. (Branching logic)- if option “c” is selected: Which immunosuppression modification do you recommend?

Pick one option:

a. Reduction in immunosuppression dosing
b. Switch to mTOR inhibitor
c. I leave it up to the transplant team to decide
d. Other: (please state)

7a - 4. (Branching logic) - if option “d” is selected, please route respondent to 7a-2 and 7a-3

[Please have participants “check through” this box prior to proceeding] Introductory stem to next section: For the next two questions (8 & 9), please consider the following scenario: A patient is noted to have **5 low-risk (AJCC 8th Edition T1/BWH T1) cutaneous SCC diagnosed over the past 5 years.** The tumor has recently been appropriately cleared by surgery with negative margins. The tumors have all been appropriately cleared by surgery with negative margins.

8. Now consider that the patient is an **abdominal (liver, kidney and/or pancreas) transplant recipient.** Which of the following medical management options for the prevention of further new skin cancers do you recommend?

   Pick one option:

   a. Observation only
   b. Add oral chemoprevention (e.g. acitretin, nicotinamide) without making changes to immunosuppression
   c. Speak with the transplant team regarding immunosuppression modification without adding oral chemoprevention
   d. Add oral chemoprevention AND speak with the transplant team regarding immunosuppression modification
   e. Other: (please state)

Other: Speak with txp team regarding immunosuppressive and apply combinations field treatments in regular intervals

8a–1. if option “a” or “e” is selected, no further questions.

8a–2. (Branching logic) - if option “b” is selected: Which oral chemoprevention do you recommend?

Pick as many options as needed to capture your recommendation. For example, if you would recommend both nicotinamide and acitretin select both a and b.

a. Add oral nicotinamide
b. Add oral acitretin
c. Other (please state)

8a -3. (Branching logic)- if option “c” is selected: Which immunosuppression modification do you recommend?

Pick one option:

a. Reduction in immunosuppression dosing
b. Switch to mTOR inhibitor
c. I leave it up to the transplant team to decide
d. Other: (please state)

8a - 4. (Branching logic) - if option “d” is selected, please route respondent to 8a-2 and 8a-3.

9. Now consider that the patient is a **thoracic (lung and/or heart) transplant recipient.** Which of the following medical management options for the prevention of further new skin cancers do you recommend?

Pick one option:

a. Observation only
b. Add oral chemoprevention (e.g. acitretin, nicotinamide) without making changes to immunosuppression
c. Speak with the transplant team regarding immunosuppression modification without adding oral chemoprevention
d. Add oral chemoprevention AND speak with the transplant team regarding immunosuppression modification
e. Other: (please state

9a–1. if option “a” or “e” is selected, no further questions.

9a–2. (Branching logic) - if option “b” is selected: Which oral chemoprevention do you recommend?

Pick as many options as needed to capture your recommendation. For example, if you would recommend both nicotinamide and acitretin select both a and b.

a. Add oral nicotinamide
b. Add oral acitretin
c. Other (please state)

9a -3. (Branching logic)- if option “c” is selected: Which immunosuppression modification do you recommend?

Pick one option:

a. Reduction in immunosuppression dosing
b. Switch to mTOR inhibitor
c. I leave it up to the transplant team to decide
d. Other: (please state)

9a - 4. (Branching logic) - if option “d” is selected, please route respondent to 7a-2 and 7a-3

10. Consider a patient who presents with a recent diagnosis of his/her **first cutaneous SCC, a high-risk (AJCC 8th Edition T3/BWH T2b) tumor**. The tumor has already been appropriately cleared by surgery with negative margins. Which of the following medical management options for the prevention of further new skin cancers do you recommend?

Pick one option:

a. Observation only
b. Add oral chemoprevention (e.g. acitretin, nicotinamide) without making changes to immunosuppression
c. Speak with the transplant team regarding immunosuppression modification without adding oral chemoprevention
d.Add oral chemoprevention AND speak with the transplant team regarding immunosuppression modification
e. Other: (please state)

10a-1 – if option “a” or “e” is selected, no further questions.

10a-2 - (Branching logic) - if option “b” is selected: Which oral chemoprevention do you recommend?

Pick as many options as needed. For example, if you would recommend both nicotinamide and acitretin select both a and b.

a. Add oral nicotinamide
b. Add oral acitretin
c. Add oral capecitabine
d. Other (please state)

10a-3. (Branching logic)- if option "c" is selected: Which immunosuppression modification do you recommend?

Pick one option:

a. Reduction in immunosuppression dosing
b. Switch to mTOR inhibitor
c. I leave it up to the transplant team to decide
d. Other: (please state)

10a-4. (Branching logic) - if option "d" is selected, please route respondent to 8a-2 and 8a-3

11. In Round 2, we achieved consensus for the use of **oral chemoprophylaxis** AND **speaking to the transplant team about immunosuppression modification** for a patient with a low rate of low-risk CSCC formation (e.g., **5 low-risk (AJCC 8th Edition T1 or BWH T1) cutaneous SCC over the past 5 years**) who then present with **a high-risk, AJCC T3/BWH T2b CSCC.** Consider you have such a patient in your clinic, and you plan to begin oral chemoprevention. Which **oral chemoprevention strategy** do you recommend?

    Pick as many options as needed to capture your recommendation. For example, if you would recommend both nicotinamide and acitretin select both a and b.

    a. Add oral nicotinamide
    b. Add oral acitretin
    c. Add oral capecitabine
    d. Other (please state)

Part 2: Non-stage based questions

12.Please rank these treatment options in terms of efficacy (**assuming complete patient compliance with each regimen**)**:**

a. Field topical 5-FU with or without another modality (e.g., curettage, retinoid, calcipotriene)
b. Field topical Imiquimod
c. Field PDT (Red or blue light, in office or daylight)
d. Other: Please state

13.Please rank these treatment options in terms of perceived compliance (**For the purpose of this exercise, assume that the clearance rates of all treatments are equal**):

a. Field topical 5-FU with or without another modality (e.g., curettage, retinoid, calcipotriene)
b. Field topical Imiquimod
c. Field PDT (Red or blue light, in office or daylight)
d. Other: Please state

14. Open ended: how do you balance efficacy v. compliance when treating with field therapy in this patient population?

15.Open ended: What do you do to try to enhance compliance when treating with field therapy in this patient population?

16.Under which of the following circumstances would you begin to routinely begin to recommend nicotinamide to transplant patients?

Select all that apply:

a. Randomized controlled trial showing a 10% reduction in SCC in OTR with a history of SCC
b. Randomized controlled trial showing a 30% reduction in SCC in OTR with a history of SCC
c. Randomized controlled trial showing a 50% reduction in SCC in OTR with a history of SCC
d. Randomized controlled trial showing a 10% reduction in future SCC in OTR with no history of SCC
e. Randomized controlled trial showing a 30% reduction in future SCC in OTR with no history of SCC
f. Randomized controlled trial showing a 50% reduction in future SCC in OTR with no history of SCC

17. When approaching the transplant team regarding IS modification, which of the following adjustments do you recommend?

Select all that apply:
a.I do not make a specific immunosuppression modification recommendation
b. Reduction or discontinuation of AZA if applicable
c.Reduction or discontinuation of CNI if applicable
d.Reduction or discontinuation of MMF if applicable
e.Convert to mTOR inhibitor

f.This is not applicable to me, as I do not approach the transplant team regarding IS modification

Part 3: Barriers to implementation questions

18. In Round 2, there was no consensus regarding field therapy modality for field cancerization despite a randomized controlled trial demonstrating superiority of 5FU-based therapy over other treatment modalities in the immunocompetent population (see NEJM article below). What do you think are the barriers to universal implementation of 5FU-based therapy given high level-of-evidence data showing benefit over other modalities?

[**attach Jansen et al article**]

Select all that apply

a. Therapy varies according to body location and extent of disease
b. Cost of 5FU-based therapy
c. Concern about patient's ability or willingness to finish treatment course
d. Patient preference for alternative therapy
e. Lack of data specifically in solid organ transplant recipients
f. Other: please state

19. In Round 2, a recommendation for initiation of nicotinamide did not achieve consensus in patients with multiple CSCC. despite an RCT demonstrating benefit in immunocompetent patients (see NEJM article below). Why do you think that a universal recommendation for nicotinamide did not achieve consensus despite this high level-of-evidence data?

[**attach Chen et al article**]

Select all that apply

a. I support use of nicotinamide in these scenarios
b. Concerns about safety in this patient population
c. Concerns about quality of studies showing benefit in the immunocompetent population
d. Insufficient data specifically in OTR for nicotinamide
e. Nicotinamide has a marginal effect in the alteration of disease progression
f. Patient preference for alternative therapy
g. Lack of widespread access to nicotinamide
h. Other: please state

20. In Round 2, there was no consensus regarding oral chemoprevention or immunosuppression modification in a patient who developed their first CSCC. Based on randomized controlled trials, we know that early mTOR conversion prevents skin cancer formation (see NEJM article below)**.** What do you think are the barriers to universal recommendation of mTOR-based therapy?

[**attach Euvrard et al article**]

    a. I support mTOR conversion in this scenario
    b. High level of evidence-based studies do not exist for this intervention
    c. In my opinion, managing immunosuppression should be left to the transplant team
    d. In my experience, the transplant team usually view mTOR therapy to be associated with too many side effects
    e. My transplant colleagues are not open to any suggestions regarding immunosuppression management
    f. Other: please state

21. In Round 2, there was consensus supporting immunosuppression modification in patients with a high rate of low-risk CSCC formation. However, there was no clear consensus on the specific immunosuppression modification recommended. Given the data cited above, what do you think are the barriers to universal recommendation of mTOR-based therapy given clear data showing benefit in this scenario?

    a. I support mTOR conversion in this scenario
    b. High level of evidence-based studies do not exist for this intervention
    c. In my opinion, managing immunosuppression should be left to the transplant team
    d. In my experience, the transplant team usually view mTOR therapy to be associated with too many side effects
    e. My transplant colleagues are not open to any suggestions regarding immunosuppression management
    f. Other: please state

22. Please write add any other considerations you might have regarding treatment options for medical management of skin cancer prevention in SOTR: