#1 – What’s New in... Skin Cancer Rates

**Incidence and prevalence of BCC and locally advanced BCC**

- Review of an national insurance claims database
- 56,987 patients with BCC were identified (39,035 incident cases; 17,952 prevalent cases).
- Age-adjusted BCC incidence and prevalence were 226.09 and 342.64 per 100,000 persons, respectively.
- These values project to 542,782 patients (incidence) and 822,593 patients (prevalence) in the 2012 US population.
- LABCC projected US incidence and prevalence: 4399 and 7940 patients

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**SCC Incidence Trends – Southern US**

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**Cancer USA - 2018**

More Skin Cancers than all other cancers combined
**SCC US 2012**

- Precise number of CSCC not well determined – 2012 data
  - CSCC cases 18 - 42K in whites
  - 5600 - 12600 nodal mets
  - 3200 - 8700 deaths

- Conclusion:
  - CSCC is an under recognized health issue. In the central and southern United States, deaths from CSCC may be as common as deaths from renal and oropharyngeal carcinomas, and melanoma

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**Melanoma - USA 2018**

- Invasive = 91,270
- In-situ = 87,290

---

**Melanoma – US 2018**

- Invasive = 91,270
- In-situ = 87,290

---

**Leading Sites of New Cancer Cases – 2010 Estimates**

<table>
<thead>
<tr>
<th>Site</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>194,929</td>
<td>49%</td>
</tr>
<tr>
<td>Lung</td>
<td>156,424</td>
<td>14%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>14,266</td>
<td>2%</td>
</tr>
<tr>
<td>Breast</td>
<td>10,922</td>
<td>1%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>9,020</td>
<td>1%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>2,790</td>
<td>1%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>3,950</td>
<td>1%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3,500</td>
<td>1%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>1,600</td>
<td>1%</td>
</tr>
<tr>
<td>All sites</td>
<td>858,270</td>
<td>100%</td>
</tr>
</tbody>
</table>

Siegel et al, Ca J Clinicians, 2018
#2 – What’s New in...
Skin Cancer Risk Factors

Phosphodiesterase type 5 (PDE5) inhibitors and MM risk
Meta-analysis

- 5 observational studies reviewed
- PDE5 use was slightly but significantly associated with increased MM risk (OR=1.12).
- Conclusions:
  - PDE5 usage directly correlated with MM development but at a low level.
  - Well conducted prospective studies needed to confirm association

Association of hydrochlorothiazide use with risk of NMSC

- Cases of NMSC diagnosed from 2004-2012 identified in the Danish Cancer Registry and matched 1:20 to controls by age and sex
- Linked to cumulative HCTZ use (from 1995-2012) from the Danish Prescription Registry
- High use of HCTZ (≥50,000 mg) associated with higher incidence of BCC (OR 1.29, 95% CI 1.23-1.35) and SCC (OR 3.98, OR 3.68-4.61) with a clear dose-response relationship
- Use of other diuretics and antihypertensives was not associated with NMSC

Association of hydrochlorothiazide use with risk of NMSC

Fig 2. Dose-response pattern between cumulative hydrochlorothiazide dose and risk of basal cell carcinoma (A) and squamous cell carcinoma (B). Error bars represent 95% confidence intervals.
Association of hydrochlorothiazide use with risk of NMSC

• Cases of NMSC diagnosed from 2004-2012 identified in the Danish Cancer Registry and matched 1:20 to controls by age and sex
• Linked to cumulative HCTZ use (from 1995-2012) from the Danish Prescription Registry
• High use of HCTZ (≥50,000 mg) associated with higher incidence of BCC (OR 1.29, 95% CI 1.23-1.35) and SCC (OR 3.98, OR 3.68-4.61) with a clear dose-response relationship
• Use of other diuretics and antihypertensives was not associated with NMSC
• Conclusions:
  -- HCTZ, a known photosensitizing agent, appears to be associated with a substantially increased, cumulative dose-dependent risk of NMSC, particularly SCC
  -- Future studies should assess and control for sun exposure, data for which was not available in this registry study

Pedersen et al. JAAD, 2017

All-cause mortality in patients with NMSC

• Meta-analysis of 12 studies looking at all-cause mortality in pts diagnosed with BCC and SCC
• Included 464,230 BCC and 175,849 SCC pts overall
• Compared with the general public, relative risk of all-cause mortality was 0.92 (95% CI 0.83-1.02) in BCC pts and 1.25 (95% CI 1.17-1.32) in SCC pts

Wehner et al. JAAD, 2017

#3 – What’s New in...
Skin Cancer Prevention

Primary vs Secondary Prevention

Primary = Protection  Secondary = Early Detection

Impact → Incidence  Impact → Mortality
What can we conclude from this data?

- Secondary prevention efforts appear to be making an impact
- Primary prevention not as impactful
- Focus of our efforts on primary prevention – behavioral change

Oral green tea catechins do not provide photoprotection from direct DNA damage induced by higher dose solar simulated radiation

- Double-blind, randomized, placebo-controlled trial in healthy white adults (13 male, 37 female; Skin types I and II) who received 1080 mg GTC (equivalent to 5 cups/day) with 100 mg vitamin C (n = 25) vs placebo maltodextrin (n = 25) daily for 12 weeks
- No difference between active and placebo groups in number of CPD-positive cells in UVR-irradiated epidermis at 24 hours
- Evaluation of a moderate (2MED) UVR dose and further time points similarly found no effect of supplement on CPD
- Conclusions:
  - Oral green tea catechins did not lower UV induced DNA CPD formation.

Oral green tea catechins do not provide photoprotection from direct DNA damage induced by higher dose solar simulated radiation

Does SPF>50 provide additional benefit?

METHODS

- 199 healthy men and women ≥18 years of age participated in a one day split face, randomized, double blind study in Vail, Colorado.
- The difference in sunburn protection provided by two currently available sunscreens (SPF 50+ and SPF 100+) was evaluated.
- Products were supplied in a kit containing two overwrapped tubes of sunscreen marked “right” and “left.” Each subject wore both sunscreens simultaneously, with product application randomized to either the right or left side of the face.
- Subjects utilized the sunscreens as they would normally during ski activities. Diaries were used to record sun exposure time and the frequency and timing of sunscreen re-applications.
- Subjects reported the next morning for clinical evaluation.
RESULTS
Primary Endpoint

SPF 50 side of face 11x more likely to be sunburned than SPF 100 side

Erythema progression was observed to be more than twice as severe on the SPF 50 vs SPF 100 protected side

The number of sunscreen reapplications was not observed to diminish the enhanced protection benefit of the SPF 100 product

SPF 100 sunscreen was significantly more effective at protecting against sunburn in all examined skin types

RESULTS
Usage

Average Product Application Density

No differences were observed in usage, application density, or reapplication frequency of the study products
CONCLUSIONS

• The SPF 100+ sunscreen was significantly more effective in protecting against sunburn than the SPF 50+ sunscreen for all skin types evaluated.

• These findings demonstrate that there is a need for sunscreens labelled with SPFs greater than 50+ to provide consumers with better choices for sunburn protection.

Polypodium leucotomos
Decreases UV induced skin damage

• Investigated Photoprotective effects of oral administration in 9 patients.

• Measured erythema (MED) and biopsied skin and measured sunburn cells, pyrimidine dimers, dermal mast cell infiltration and Langerhans cells.

• All of these measures were improved with the administration of polypodium.

• Conclusion:
  - Effective systemic chemoprotective agent against UV radiation exposed skin damage.

Williams et al, JAAD, 2018

Polypodium leucotomos
Decreases UV induced skin damage

UV-induced Cyclobutane Pyrimidine Dimers

UV induces:
• Cyclobutane pyrimidine dimers (CPDs, T-T abnormal nucleotide binding).
• A defect known as 6-pyrimidine-4-pyrimidone (6-4 PP).

Both effects distort the helix, and alter replication.

UV-induced cyclobutane pyrimidine dimers, characterized by new connection between thymidine nucleotide bases and break between uniform A-T binding.1,2

A=adenine, T=thymidine, S=sugar-phosphate base of helix


After UVA exposure photolyase identifies the Defective DNA

Potential Benefit of Photolyses when Exogenously Applied

• Almost half of the thymidine dimers can be repaired.

• Humans have other endogenous repair mechanisms such as T4N5 endonuclease, which are less efficient.

• Exogenously applied photolases have potential benefits1,2.


A=adenine, T=thymidine, S=sugar-phosphate base of helix
Differences in the mean rate of production of AK and NMSC over a one year treatment time with sunscreen containing photolyases.

Photolyase containing sunscreens have the potential to reduce production of AKs and NMSC

Chemoprevention of BCC and SCC with a single course of 5-FU Cream

- 932 VA pts with history of ≥2 keratinocyte cancers within 5 years recruited
- Randomized to 5-FU cream vs vehicle to face and ears bid x4 weeks
- Treatment arm experienced 75% reduction in SCC (p=0.002) and 11% reduction in BCC (p=NS) over 1 year of follow-up
- No difference between treatment and vehicle groups in time to first SCC or BCC

Promoting sunscreen use and sun-protective practices in NCAA athletes: Impact of educational intervention

- 846 National Collegiate Athletic Association student athletes (SA) were surveyed between September 23, 2012, and September 20, 2015.

- After intervention, significant increases were observed in:
  - Sunscreen use 4 or more days per week by SAs (from 26% to 39% [P = .02]),
  - SAs spoken to by their coach about sun safety (from 26% to 57% [P = .0001]),
  - SA recognition of higher skin cancer risk (from 54% to 67% [P = .04]).

- Conclusions:
  - This study emphasizes that education directed to SAs, ATs, and coaches can improve sun-protective practices in SAs.
#4 – What’s New in...
Skin Cancer Prognosis

Prognostic models for cSCC mets

- Data on 800 cSCCs from 585 patients

<table>
<thead>
<tr>
<th>Anatomic location</th>
<th>Tumor diameter defined as high-risk by anatomic location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>≤ 2 cm</td>
</tr>
<tr>
<td>Legs</td>
<td>&gt; 2.5 cm</td>
</tr>
<tr>
<td>Neck</td>
<td>&gt; 4 cm</td>
</tr>
<tr>
<td>Extremities</td>
<td>&gt; 3 cm</td>
</tr>
</tbody>
</table>

Fosko et al, SKIN, 2017

Prognostic Risk Factors

- Meta-analysis of 36 CSCC studies (17, 248 pts)
- Significant risk factors for metastasis were:
  - Invasion beyond subcutaneous fat (RR=11.2)
  - Breslow thickness >2mm (RR=10.7)
  - Breslow thickness >6mm (RR=6.9)
  - Diameter >20mm (RR=4.5)
  - Poor differentiation (RR=4.1)
  - Perineural invasion (RR=2.9)
  - Immunosuppression (RR=1.8)
  - Temple, lip or ear location (RR=2.8)

Thompson et al, JAMA Dermatol, 2016

Prognostic Risk Factors

- Meta-analysis of 36 CSCC studies (17, 248 pts)
- Significant risk factors for Disease-Specific Death were:
  - Diameter >20mm (RR=19.1)
  - Poor differentiation (RR=5.6)
  - Ear location (RR=4.6)
  - Lip location (RR=4.5)
  - Invasion beyond subcutaneous fat (RR=4.5)
  - Perineural invasion (RR=4.1)

Thompson et al, JAMA Dermatol, 2016

SCC Prognostic Risk Factors

- Conclusion:
  - Tumor depth is associated with the highest RR of local recurrence and cSCC metastasis and tumor diameter >20mm associated with the highest RR of DSD.
  - Unified, consistent collection and reporting of risk factors in a prospective, multicentered effort are needed to further understand the increasing incidence of cSCC

Thompson et al, JAMA Dermatol, 2016
SCC Prognostic Risk Factors

- Meta-analysis of 36 CSCC studies (17, 248 pts)
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  - Tumor depth is associated with the highest RR of local recurrence and cSCC metastasis and tumor diameter >20mm associated with the highest RR of DSD.
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Thompson et al., JAMA Dermatol, 2016

Depth and diameter are an indirect measure of Volume

Similar findings in melanoma

Mossbacher et al., JID, 1996

MSLT II: Completion dissection vs observation in SLNBx+ MM Pts

- International, randomized trial
- 1,934 melanoma, SLNBx+ pts randomized to completion lymph node dissection vs nodal observation with ultrasound
- Mean 3-year melanoma-specific survival rate similar between dissection and observation groups (86±1.3% vs 86±1.3%, p=0.42) with median f/u of 43 months
- Disease-free survival slightly higher in the dissection group vs the observation group at 3 years (68±1.7% vs 63±1.7%, p=0.05)
- Lymphedema observed in 24.1% of the dissection group vs 6.3% of the observation group

Faries et al., JAMA Dermatol, 2017

Conclusions:
- Immediate completion LN dissection increases the rate of regional-disease control but does not increase melanoma-specific survival in SLNBx+ melanoma patients

Faries et al., JAMA Dermatol, 2017
**Impact of surgical timing on survival in cutaneous melanoma**

- 153,218 patients with stage I-III melanoma in the National Cancer Database were assessed
- On multivariate analysis stratified by stage, increased time from biopsy to surgery increased mortality risk in stage I pts relative to those treated within 30 days
  - 30-59 days (HR 1.05, 95% CI 1.01, 1.11)
  - 60-89 days (HR 1.16, 95% CI 1.07, 1.25)
  - 90-119 days (HR 1.29, 95% CI 1.12, 1.48)
  - >119 days (HR 1.41, 95% CI 1.21, 1.65)

**Conclusions:**
- Surgical timing did not significantly impact survival in stage II/III disease
- Definitive treatment of stage I melanoma within 30 days improves patient survival

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**#5 – What’s New in…**

**NMSC Management**

**Topical diclofenac 3% and calcitriol 3 μg/g for sBCC and nBCC treatment**

- Histologically proven sBCC (n = 64) or nodular BCC (n = 64) were randomized to topical diclofenac, calcitriol, combination of both, or no topical treatment (control group).
- After self-application twice daily under occlusion (8 weeks), tumors were excised.
- Complete histologic tumor regression was seen in 64.3% (P = .0009) of sBCC (diclofenac) and 43.8% (P = .007) of sBCC (combination tx) vs. 0% of controls.
- No significant changes were found in nodular BCC.
- Application-site reactions were mostly mild to moderate.
- Conclusion:
  - Results suggest that topical diclofenac is a promising new treatment for sBCC.
  - Mode of action differs from available noninvasive therapies, and thus has an additive value.

**Phase II, randomized, double-blind study of sonidegib in patients with advanced BCC**

- Multicenter, randomized, double-blind phase II study, 230 patients were randomized 1:2 to sonidegib 200 or 800 mg.
- Response rates in the 200- and 800-mg arms were 57.6% and 43.8% in locally advanced BCC and 7.7% and 17.4% in metastatic BCC, respectively.
- Among the 94 patients with locally advanced BCC who responded, only 18 progressed or died and more than 50% had responses lasting longer than 6 months.
- 4 of 5 responders with metastatic BCC maintained an objective response
**Phase II, randomized, double-blind study of sonidegib in patients with advanced BCC**

Dummer et al, JAAD, 2016

**Age at diagnosis as a relative contraindication for intervention in NMSC of the face**

- Standard excision of 569 biopsy-proven NMSC of the face (440 pts) performed
- 50.5% BCC, 30.2% SCC
- No residual cancer found on histology in 35.3% of samples
- 3-year all-cause mortality rates increased with age
  - <60 years: 3.6%
  - 60-69 years: 4.4%
  - 70-79 years: 7.6%
  - 80-89 years: 15.8%
  - >90 years: 48.1%

Chauhan et al, JAMA Surgery, 2017

**Risk of cutaneous SCC after treatment of BCC with vismodegib**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with vismodegib (yes vs no)</td>
<td>0.97 (0.93-1.01)</td>
<td>0.22</td>
</tr>
<tr>
<td>Age at basal cell carcinoma treatment (&lt;60 vs ≥60 years)</td>
<td>2.96 (2.17-4.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>1.79 (1.30-2.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of nonmelanoma skin cancer (yes vs no)</td>
<td>1.66 (1.26-2.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Office visits per year</td>
<td>1.06 (1.01-1.11)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Conclusion: Vismodegib was not associated with an increased risk of subsequent SCC when compared with standard surgical treatment of BCC

Bhutani et al, JAAD, 2017

**2 intermittent vismodegib dosing regimens in patients with multiple BCCs**

Dreno et al, Lancet Oncol, 2017
2 Intermittent vismodegib dosing regimens in patients with multiple BCCs

- Mean number of basal-cell carcinoma lesions at the end of treatment (week 73), was reduced from baseline in both groups:
  - 62.7% (95% CI 53.0–72.3) in treatment group A
  - 54.0% (43.6–64.4) in treatment group B.
- The number of treatment-emergent adverse events in treatment group B was higher, adherence to treatment was lower, and treatment activity was less than in treatment group A.

- Conclusion:
  Because the on-target side-effects of vismodegib might hamper lifelong treatment, the acceptability of systemic intermittent treatment with this drug warrants further investigation.

Dreno et al, Lancet Oncol, 2017

Age at diagnosis as a relative contraindication for intervention in NMSC of the face

- Standard excision of 569 biopsy-proven NMSC of the face (440 pts) performed
  - 55.5% BCC, 30.2% SCC
- No residual cancer found on histology in 35.3% of samples
- 3-year all-cause mortality rates increased with age
  - <60 years: 3.6%
  - 60–69 years: 4.4%
  - 70–79%: 7.6%
  - 80–89 years: 19.8%
  - >90 years: 48.1%

- Conclusions:
  - The 3-year survival rate following facial NMSC excision in pts over age 90 is ~52%, and a proportion of pts had no residual disease on excision pathology following initial biopsy
  - These issues should be discussed with patients and future studies should investigate watchful-waiting as an approach in elderly patients

- Caveats:
  - Pts >90 years of age do not necessarily represent a homogenous population
  - Authors make the point that no pt in this study died from NMSC-related causes, but it should be noted that all included pts underwent excision

Chauhan et al. JAMA Surgery, 2017

#6 – What’s New in...
Skin Cancer Diagnostic Devices

- EIS is a measure of the overall resistance within a tissue at alternating currents of various frequencies
- EIS is measured by applying an unnoticeable and harmless alternating electrical current onto the skin and measure the response
- The platform consists of a handheld probe with a disposable electrode connected to a device analyzing the signals
- Disposable electrode can be used up to 20 times per patient and must be changed between patients

Electrical Impedance Spectroscopy (EIS) method
**Principle of EIS**

- The pins penetrate into the stratum corneum. Impedance is measured in the viable skin under stratum corneum.
- Alternating current is transmitted from one electrode bar to another at 35 predefined frequencies that relate to clinically relevant properties in the skin.
- In order to cover the lesion in both width and depth, the measurement is performed in 10 permutations covering both shallow as well as deeper measurements.
- Amplitude and phase shift in the resulting signal are measured at the receiving electrode bar.

**EIS correlation to severity of lesions**

- EIS correlation to the stage of lesion severity is shown in the box plot from the pivotal study.
- There is a very distinct step function in the output, correlated to the stage of the lesion – from benign to a late stage invasive melanoma – clearly confirming the ability of the technology to identify malignant parameters.

**Assessing Margins in Mohs**

- Reliance of Mohs micrographic surgery (MMS) technique on histologic margin assessment at each stage significantly adds to procedure duration.
- Bioimpedance spectroscopy is a novel ex vivo technique that has been used to differentiate benign from malignant tissues, and has been applied to intraoperative surgical margin assessment during the removal of urologic malignancies.
- Objective: To assess the sensitivity and specificity of bioimpedance spectroscopy for determining positivity of MMS specimens of non-melanoma skin cancer (NMSC).

**Cole Relaxation Frequency**
**Results**

<table>
<thead>
<tr>
<th>Likelihood of Containing Malignant Cells by Cole Analysis</th>
<th>Number of Occurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unlikely→ FC &lt; 1x10⁵</td>
<td>0</td>
</tr>
<tr>
<td>Likely→ 1x10⁵ ≤ FC ≥ 2x10⁶</td>
<td>15</td>
</tr>
</tbody>
</table>

Svoboda et al, JAAD Submitted

**Conclusions**

- Bioimpedance spectroscopy demonstrated high sensitivity and specificity (compared to frozen histopathology) assessing the margins of NMSC MMS specimens in this pilot sample.
- Combined with the short duration of bioimpedance measurements (~7 seconds per specimen) and minimal training required, these findings suggest that bioimpedance has the potential to reduce case time while maintaining high diagnostic accuracy.
- Larger, multicenter studies are recommended to increase the generalizability of these results.

---

**How Reflectance Confocal Microscopy Works**

**In Vivo Confocal Microscopy Multistep Algorithm to Detect MMIS**

- To identify RCM (reflectance confocal microscopy) features of MMIS and to develop a diagnostic score for MMIS while combining dermoscopy and RCM.
- 120 MMIS and 213 lesional test set were retrospectively analysed to assess the presence of dermoscopic and RCM criteria.
- Multivariate results on the test set allowed the development of a multistep algorithm, that was tested on a validation set consisting of 100 lesions.
- A multistep diagnostic algorithm able to predict MMIS with a sensitivity of 92.5% and a specificity of 61% was developed.
- Validation set confirmed the high diagnostic value (sensitivity 92%, specificity 58%).
- Conclusions: Reproducible multi-step algorithm for MMIS detection developed that can be routinely used in tertiary centers.

---

**In Vivo Confocal Microscopy Multistep Algorithm to Detect MMIS**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical network</td>
<td>+1</td>
</tr>
<tr>
<td>Regression</td>
<td>+1</td>
</tr>
<tr>
<td>Pagetoid cells</td>
<td>+1</td>
</tr>
<tr>
<td>Cytologic atypia</td>
<td>If focal =+1, if widespread =+2</td>
</tr>
<tr>
<td>Desmocytic</td>
<td>-1</td>
</tr>
<tr>
<td>Melanophages</td>
<td>-1</td>
</tr>
</tbody>
</table>

A total score of 2 or higher precipitated a recommendation of excision.

---

**Borsari et al, Br J Dermatol, 2018**
In Vivo Confocal Microscopy Multistep Algorithm to Detect MMIS

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- Conclusions:
  - Reproducible multistep algorithm for MMIS detection developed that can be routinely used in tertiary centers.

Borsari et al, Br J Dermatol, 2018

What does the 23 genetic expression profile (23-GEP) test do?

- Premise: Benign and malignant melanocytic lesions behave differently (invasion, metastasis, immune function etc.) and this is associated with expression of different (and/or different amounts of) RNAs.
- Identified a panel of 23 genes that are differentially expressed in benign and malignant melanocytic lesions and has developed a myPath test that:
  - purifies RNA from tissue
  - quantifies how much of each of the 23 RNAs is expressed
  - applies a mathematical algorithm to objectively determine if the lesion is benign or malignant based on the expression pattern

Benign

Melanoma

Clinically or Histologically Uncertain Pigmented Lesion

#7 – What’s New in...
Genetics in Skin Cancer Diagnosis and Prognosis

What does the 23 genetic expression profile (23-GEP) test do?

Summary

- Three clinical validation studies encompassing over 1,300 melanocytic neoplasms demonstrate overall accuracy of >90%, including:
  - Over 300 melanocytic lesions with proven outcomes
  - Overall sensitivity: 90-94%
  - Overall specificity: 91-96%
  - Increases Definitive Diagnoses
  - Impacts Patient Treatment Decisions

Noninvasive 2-gene molecular assay for cutaneous melanoma

- Evaluated and validated in 555 pigmented lesions (157 training and 398 validation samples) obtained noninvasively via adhesive patch biopsy.
- Results were compared with standard histopathologic assessment.
- Differentiated melanoma from nonmelanoma samples with a sensitivity of 91% and a specificity of 69%

Gerami et al. JAAD. 2017

Gerami et al. JAAD. 2017
**Pigmented Lesion Assay Results**

Performance of LINC00518 and/or preferentially expressed antigen in melanoma detection in the validation set.

<table>
<thead>
<tr>
<th>Biology of sample</th>
<th>Pathologically confirmed</th>
<th>Neither of the 2 genes detected</th>
<th>1 of the 2 genes (LINC or PRAME) detected</th>
<th>Both LINC and PRAME detected</th>
<th>Detection (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>87</td>
<td>8</td>
<td>13</td>
<td>66</td>
<td>91% (87%-94%)</td>
</tr>
<tr>
<td>Nonmelanoma</td>
<td>311</td>
<td>215</td>
<td>63</td>
<td>35</td>
<td>69% (64%-73%)</td>
</tr>
<tr>
<td>Total</td>
<td>398</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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- Evaluated and validated in 555 pigmented lesions (157 training and 398 validation samples) obtained noninvasively via adhesive patch biopsy.
- Results were compared with standard histopathologic assessment.
- Differentiated melanoma from nonmelanoma samples with a sensitivity of 91% and a specificity of 69%.
- Conclusion: Assay classifies pigmented lesions into melanoma and nonmelanoma groups and may serve as a tool to help with diagnostic challenges.

**What is the Melanoma Gene Expression Profile Test (31-GEP)**

- Identifies a genomic profile, not genetic mutations.
- Validated proprietary 31-gene expression profile test.
- Uses in formalin-fixed, paraffin-embedded tissue specimen obtained from primary biopsy.
  - That is, no special processing on behalf of the dermatologist or dermatopathologist.

**GEP Test Workflow**

- RNA isolation
- cDNA generation and amplification (14X)
- Microfluidics PCR gene card
- 28 discriminant gene targets and 3 control genes
- Analysis of GEP with a proprietary algorithm to determine class and metastatic risk
- Class 1: low 5-year metastatic risk
- Class 2: high 5-year metastatic risk

**31-GEP Test Melanoma Analysis with SLNBx Status**

- This analysis shows that both SLNB positive status and 31-GEP Melanoma Class 2 are important predictors of DMFS and OS.
- SLNB identified ~30% of patients who died, but 70% of patients who died were SLNB negative.
- Performing the 31-GEP Melanoma assay in the SLNB negative cohort identified over 80% of those SLNB negative patients who developed distant metastasis and died.
If SNLBx is Negative, 31-GEP Status is Predictive of Prognosis

**What's New With the 31-GEP Prognostic Test?**

**Can 31-GEP guide SLNB patient selection?**
- Currently, SLNB is necessary in order to consider a patient as a Stage III and eligible for adjuvant therapy interventions
- However, it is estimated that the rate of SLN positivity is 16% in the general population, which means 84% of patients do not benefit from this procedure
- Older age is associated with a poor prognosis, yet fewer elderly patients are SLN positive
- Likewise, a negative SLNB in head and neck melanomas is known to have higher recurrence rates than a negative SLNB in trunk or extremity melanomas
- There is an association between 31-GEP Class 1 and lower rates of positive SLNB results
- Could 31-GEP identify a population with ≤5% positive rate for SLNB?

**5% SLNB positivity rate is often considered an adequate threshold for considering this procedure**

**What happens to a T1/T2 patient?**

**NCCN SLNBx recommendations (1/18):**

- 0-5% SLNB+ rate = do not perform
- 5-10% SLNB+ rate = discuss and consider
- ≥10% SLNB+ rate = discuss and offer

**Impact on SLNBx: Procedures reduced by 52%**

**Can 31-GEP be used to increased the yield of SLNBx?**

**21-GEP - Cox regression analysis for cases with thin (≤1mm) tumors and SLNBx performed shows strong prognostic value in this population**

<table>
<thead>
<tr>
<th>Factors</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breslow depth</td>
<td>0.4</td>
<td>0.01-1.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Mitotic rate</td>
<td>1.1</td>
<td>0.9-1.4</td>
<td>0.25</td>
</tr>
<tr>
<td>Ulceration</td>
<td>3.2</td>
<td>1.0-14.5</td>
<td>0.06</td>
</tr>
<tr>
<td>SLN status</td>
<td>2.1</td>
<td>0.5-8.8</td>
<td>0.29</td>
</tr>
<tr>
<td>GEP Class 2</td>
<td>1.4</td>
<td>1.0-23.3</td>
<td>0.03</td>
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*The factors significant in multivariate analysis for DDS for MM.*

**What impact can 31-GEP have on SLNB procedures?**

**Can 31-GEP guide SLNB patient selection?**

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**What happens to a T1/T2 patient?**

**MSS OS DMFS RFS**

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Melanoma 31-GEP’s NPV supports guidance of SLNBx

<table>
<thead>
<tr>
<th>Test</th>
<th>Disease</th>
<th>Endpoint</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ConfirmMDx</td>
<td>Prostate cancer</td>
<td>Rule-out repeat biopsies after negative prostate biopsy</td>
<td>90%</td>
</tr>
<tr>
<td>Percepta</td>
<td>Lung cancer</td>
<td>Rule-out massive procedures after bronchoscopy</td>
<td>91%</td>
</tr>
<tr>
<td>Afirma</td>
<td>Thyroid cancer</td>
<td>Rule-out surgery for indeterminate thyroid nodules</td>
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<tr>
<td>Melanoma</td>
<td>Cutaneous melanoma</td>
<td>Rule-out SLNB biopsy in cutaneous melanoma</td>
<td>96%</td>
</tr>
</tbody>
</table>

*50% poor risk patients

Genetic Factors impacting on cSCC

- MC1R gene variants (by way of leading to light skin complexion)
- Mutations in p53 tumor suppressor gene
- Aberrant activation of EGFR and Fyn
- RAS activating mutations seen in 21% off cases (9% Hras, 7% Nras, 5% Kras)

Stratigos et al, Eur J Cancer, 2015

Gene expression comparison in recurrent vs. non-recurrent subjects

- 18 genes have already demonstrated significant differential expression in recurrent cases compared to non-recurrence cases
- Pathway analysis shows these genes to be relevant to tumor aggressiveness (recurrence drivers):
  - Tissue Remodeling: transcription factors, cytoskeletal genes, receptors
  - Immune Genes: including chemokines, cytokines, and their receptors
  - Matrix metalloproteinases (MMPs): degrade extracellular matrix during process of tissue remodeling, invasion, and migration
  - AKT/mTOR, B-Raf/MAP/MEK: pro-growth pathways that regulate invasion, remodeling, and growth
- Result: one of the most frequently mutated genes in SCC, targets p21, MYC, and the HES-family, linked to the TP53 pathway

Clinical Research Comparison: Cutaneous Melanoma vs SCC

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<tr>
<th>Melanoma</th>
<th>SCC</th>
</tr>
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<tbody>
<tr>
<td>Artifical Intelligence (neural network) modeling identified several promising algorithms</td>
<td></td>
</tr>
<tr>
<td>Average model demonstrated improved sensitivity and maintained NPV</td>
<td></td>
</tr>
<tr>
<td>Next steps: Complete validation</td>
<td></td>
</tr>
</tbody>
</table>

Initial GEP Algorithm Shows Improved Sensitivity to Identifying Likelihood of Recurrence and Maintaining high Negative Predictive Value (NPV)

- Out of 68 putative discriminating genes...
- Gene expression shows these genes to be relevant to tumor aggressiveness (recurrence drivers):
  - Tissue Remodeling: transcription factors, cytoskeletal genes, receptors
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Question:

Can the Genetic Expression Profile (GEP) of primary SCC tumor identify aggressive disease like it does in cutaneous melanoma?...

Answer:

Yes. But there is work to do...

Clinical factors:

- MC1R gene variants (by way of leading to light skin complexion)
- Mutations in p53 tumor suppressor gene
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#8 – What’s New in...
Melanoma Follow Up Regimens

Risk of subsequent melanoma after MMIS and invasive MM

- From 1973 to 2011, 55,661 MMIS and 112,613 with invasive MM as their first primary cancer of any type and as their first primary cancer
- 5817 individuals (3.5%) developed at least 1 subsequent melanoma in situ. Incidence rate of subsequent melanoma in situ was 3.8 per 1000 person-years.
- 6067 individuals (3.6%) developed at least 1 subsequent invasive melanoma. Incidence rate of subsequent invasive melanoma was 3.7 per 1000 person-years.
- Is that higher than the general population?

Risk of Developing MM

Melanoma Incidence

- Annual incidence per 100K

Risk of subsequent melanoma after MMIS and invasive MM

- Cumulative lifetime risk for subsequent melanoma approached 20%

Conclusions:
Melanoma patients need to be followed closely for:
- Risk of spread of disease from their initial tumors
- Risk of development of additional primary melanomas
Should SLNBx be performed?

NCCN SLNBx recommendations (2018):
- 0-5% SLNB+ rate = do not perform
- 5-10% SLNB+ rate = discuss and consider
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 ASCO guidelines update on SLNBx and management of regional LNs in MM

- Guidelines updated based on interval publication of:
  - 9 observational studies
  - 2 systematic reviews
  - 2 updated randomized, controlled trials
    - Multicenter Selective Lymphadenectomy II (MSLT-II)
    - German Dermatologic Oncology Cooperative Group (DeCOG-SLT)
- Sought to address 2 key questions:
  - What are the indications for SLNBx?
  - What is the role of completion lymph node dissection?

NCCN SLNBx recommendations (2018):
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**ASCO guideline update on SLNBx and management of regional LNs in MM**

**Key Recommendations**

- **Thin MMs:**
  - Routine SLNBx is not recommended for patients with MM that are T1a (non-ulcerated lesions < 0.8mm in thickness)
  - SLNBx may be considered for T1b pts (0.8 to 1.0mm or < 0.8mm with ulceration) after a thorough discussion with pt of potential benefits and risks of procedure-associated harm

- **Intermediate thickness MM:**
  - SLNBx is recommended for patients with MM that are T2 or T3 (1.0 to 4.0mm)

- **Thick MM:**
  - SLNB biopsy may be recommended for patients with MM that are T4 (> 4.0mm), after a thorough discussion with pt of potential benefits and risks of procedure-associated harm

---

**Targeting Approaches to Systemic MM**

- **BRAF inhibitors**
  - Interrupts the B-Raf/MEK step on the activation pathway if the B-Raf has the V600E mutation
- **MEK inhibitors**
  - Inhibits the mitogen-activated protein kinase enzymes MEK1 and/or MEK2
- **PD-1 blockers**
  - Programmed death 1 (PD-1) receptor is a negative regulator of T-cell effector mechanisms that limits immune responses against cancer
- **CTLA-4 antibodies**
  - CTLA-4 inhibits T cell responses

---

**Potential Advantage of Combination Therapy**

- Either CLND or careful observation may be offered to patients with low risk micrometastatic disease, with due consideration of clinicopathological factors.
- For higher risk patients, careful observation may be offered only after a thorough discussion with patients about the potential risks and benefits of NOT performing CLND

---

**Clinical Activity in Patients Receiving Concurrent Regimen of Nivolumab and Ipilimumab**

- Nivolumab + Ipilimumab result in improved clinical outcomes compared to the monotherapy arm.
Targeted Therapies for Melanoma

<table>
<thead>
<tr>
<th>BRAF</th>
<th>MEK</th>
<th>CTLA-4</th>
<th>PD-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemurafenib</td>
<td>Trametinib</td>
<td>Ipilimumab</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>Cobimetinib</td>
<td>Pembrolizumab</td>
<td>Atezolizumab</td>
</tr>
</tbody>
</table>

Targeted Antitumor Therapy

Immune Checkpoint Blockade

Epacadostat + Pembrolizumab

Change in tumor burden in patients with treatment-naive melanoma: Best percentage change in target lesions for patients with postbaseline assessments.

Pembrolizumab in combination with Dabrafenib and Trametinib

Longitudinal change from baseline in tumor size.
#10 – What’s New in...
A cure for Melanoma?

How close are we to a cure?

New immunotherapy drug behind Jimmy Carter’s cancer cure

Epidemiology
Risk Factors
Prevention
Management
Genetics
- Diagnosis
- Prognosis
- Advanced disease therapy

**Nivolumab Phase Ib 7 year Follow-up:**

Overall survival plateaus at 3 years

**Key new things in Skin Cancer that can impact on your patients**

Summary

- Epidemiology
- Risk Factors
- Prevention
- Management
- Genetics
  - Diagnosis
  - Prognosis
  - Advanced disease therapy