MELANOMA UPDATE
31 Gene Expression Profiling in Melanoma
Review of evidence supporting clinical use of 31-Gene Expression Profile
AJCC Melanoma Staging Criteria 8th Edition
# NCCN guidelines

**Individual risk of SLN positivity drives SLNB recs**

<table>
<thead>
<tr>
<th>Features</th>
<th>Chance for +SLN</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.75 and T1a</td>
<td>&lt;5%</td>
<td>NCCN</td>
</tr>
<tr>
<td>&gt;0.75, or ulceration, or</td>
<td>&gt;5%</td>
<td>MSKCC</td>
</tr>
<tr>
<td>regression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0.75 and ≥1 neg. feature</td>
<td>12.5%</td>
<td>U Penn</td>
</tr>
</tbody>
</table>

**NCCN Recommendations for SLNB (2.2018)**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>SLN+ (positivity) rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discuss and offer</td>
<td>≥10%</td>
</tr>
<tr>
<td>Discuss and consider</td>
<td>&gt;5% to 10%</td>
</tr>
<tr>
<td>Do not perform</td>
<td>≤5%</td>
</tr>
</tbody>
</table>

Han D. J Clin Oncol. 2013;31:4387
Risk of recurrence drives management decisions for melanoma patients
Management of Stage I-III melanoma patients involves making the following decisions

• Frequency of follow-up
• Frequency and modality of surveillance imaging
• Referral to Surgical Oncology
• Sentinel Lymph Node Biopsy
• Referral to Medical Oncology
• Adjuvant therapy
What’s the risk?
Staging-only approach misses patients with aggressive tumor biology

**Stage at Diagnosis**

- Stage I: 80%
- Stage II: 13%
- Stage III: 8%

*Excludes Stage IV*

**Melanoma Deaths by Stage at Diagnosis**

- Stage I: 26%
- Stage II: 40%
- Stage III: 35%

*Excludes Stage IV*
Combined cohort enables clinically relevant subgroup analyses

- **Stage I-IIA** – Considered Low Risk by NCCN guidelines with minimal follow up and no imaging recommended yet account for at least 37% of deaths*.

- **Thin Tumors** – Majority of patients have thin tumors (≤1.0mm) and these patients are considered low risk but contribute substantially to mortality.

- **Stage IIIA** – Can tumor biology inform management decisions (risk/benefit of adjuvant therapy) in Stage IIIA patients?

*from those contributed by patients with Stage I-III disease at diagnosis
The majority of deaths occur in early stage disease despite AJCC clinicopathologic factors

- Prognostic accuracy has direct implications on patient follow up
- Early intervention has consistently shown to be a significant predictor of response
- Newer therapies and regional interventions have shown effectiveness in the adjuvant setting
A 31-Gene Expression Profile (GEP) was developed to assess risk of recurrence using tumor biology independent from traditional clinico-pathologic factors.
Prospective, multi-center registry study initial analysis confirms independent prognostic value

• Two 5-year registry protocols (INTEGRATE and EXPAND) were developed in parallel to prospectively track clinical utility and outcomes

• Eleven U.S. dermatologic and surgical centers

• Enrollment began in 2014; closed in Jan 2016
  • Data updates were completed between Nov 2016 and Jan 2017
  • Study continues for remainder of 5-yr duration

• In total, 335 patients were enrolled in the studies, with 322 patients included in the Year 3 interim analysis
  • Median follow-up time for event-free patients was 1.5 years

Hsueh et al. J Hematol Oncol; 10(152), 2017
Second independent, prospective study showing consistent 31-GEP performance in dermatology practice population

- Prospectively-collected melanoma registry with chart review (n=256)
  - 86% of patients were Stage I
  - 14% were Stage II
- 16% of patients were Class 2 (high risk)
- 23-month mean follow-up time for total cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Class 1  n=214</th>
<th>Class 2  n=42</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median years)</td>
<td>68</td>
<td>77</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>130</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>84</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Follow-up time (mean months)</td>
<td>22</td>
<td>28</td>
<td>0.084</td>
</tr>
<tr>
<td>Breslow thickness (mean mm)</td>
<td>0.6</td>
<td>2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mitotic rate /mm² (mean)</td>
<td>0</td>
<td>1.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ulceration present</td>
<td>9</td>
<td>17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AJCC Stage: I</td>
<td>201</td>
<td>18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AJCC Stage: II</td>
<td>13</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

Greenhaw et al. *Dermatol Surg* 2018
31 Gene expression profiles

 Patients with Stage I-III melanoma

- Quantifies expression of 31 genes from primary tumor using RT-PCR
- Applies a validated algorithm
- Accurately classifies patients as low or high risk

Class 1:
Low risk of melanoma recurrence within 5 years

1A
Lowest risk

1B
Low risk

Class 2:
High risk of melanoma recurrence within 5 years

2A
Increased risk

2B
Highest risk
SLNB- NEGATIVE patients, 31-GEP shows independent prognostic value that complements and adds to information provided by SLNB

<table>
<thead>
<tr>
<th></th>
<th>5-year DMFS (95% CI)</th>
<th>Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLNB- (n=259)</td>
<td>82% (77-87%)</td>
<td>54 (21%)</td>
</tr>
<tr>
<td>SLNB+ (n=200)</td>
<td>51% (44-60%)</td>
<td>94 (47%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SLNB Negative</th>
<th>5-year DMFS (95% CI)</th>
<th>Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1 (n=136)</td>
<td>91% (86-96%)</td>
<td>16 (12%)</td>
</tr>
<tr>
<td>Class 2 (n=123)</td>
<td>71% (64-80%)</td>
<td>38 (31%)</td>
</tr>
</tbody>
</table>

70% of High-risk SLNB- patients were Class 2

38 of 54 SLN negative patients who had events were identified as Class 2
SLNB- POSITIVE patients, 31-GEP shows independent prognostic value that complements and adds to information provided by SLNB.

**DMFS**

- **SLNB -**
  - Class 1 SLNB
  - Class 2 SLNB

<table>
<thead>
<tr>
<th>SLNB Positive</th>
<th>5-year DMFS (95% CI)</th>
<th>Events (%)</th>
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</thead>
<tbody>
<tr>
<td>SLNB- (n=259)</td>
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<tr>
<td>SLNB+ (n=200)</td>
<td>51% (44-60%)</td>
<td>94 (47%)</td>
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</table>

<table>
<thead>
<tr>
<th>SLNB Positive</th>
<th>5-year DMFS (95% CI)</th>
<th>Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1 (n=63)</td>
<td>72% (61-85%)</td>
<td>19 (30%)</td>
</tr>
<tr>
<td>Class 2 (n=137)</td>
<td>41% (33-52%)</td>
<td>75 (55%)</td>
</tr>
</tbody>
</table>

80% of SLNB+ pts with event were Class 2

75 of 94 SLNB positive patients who had an event were Class 2
31-GEP test further informs risk obtained by AJCC 8th edition staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Risk Category</th>
<th>Melanoma-Specific Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Low Risk</td>
<td>≈IA 99.6%</td>
</tr>
<tr>
<td>II</td>
<td>Low Risk</td>
<td>≈IA 99%</td>
</tr>
<tr>
<td>III</td>
<td>High Risk</td>
<td>≈IIA 94.8%</td>
</tr>
</tbody>
</table>

NCCN Risk Category:
- Class 1A (90%)
- Class 2B (77%)
- AJCC MSS (90%)

Melanoma-Specific Survival (%) on Stage:
- Stage I: 98%
- Stage IIA/IIB: 89.5%
- Stage IIB/IIC: 84.7%
- Stage IIIC+: 61.2%
- Stage III: 77%
Cox regression analysis shows 31-GEP to be the most robust, independent prognostic indicator in Stage I-IIA (NCCN – Low Risk) patients.

<table>
<thead>
<tr>
<th>Cox Multivariate Analysis</th>
<th>RFS</th>
<th>DMFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Breslow depth</td>
<td>1.47</td>
<td>1.17-1.86</td>
</tr>
<tr>
<td>Mitotic rate</td>
<td>1.05</td>
<td>0.99-1.12</td>
</tr>
<tr>
<td>Ulceration</td>
<td>1.28</td>
<td>0.51-3.2</td>
</tr>
<tr>
<td>GEP Class 1B</td>
<td>1.67</td>
<td>0.41-6.75</td>
</tr>
<tr>
<td>GEP Class 2A</td>
<td>5.1</td>
<td>1.53-16.93</td>
</tr>
<tr>
<td>GEP Class 2B</td>
<td>7.33</td>
<td>2.65-20.26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cox Multivariate Analysis</th>
<th>MSS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
</tr>
<tr>
<td>Breslow depth</td>
<td>1.5</td>
</tr>
<tr>
<td>Mitotic rate</td>
<td>0.95</td>
</tr>
<tr>
<td>Ulceration</td>
<td>1.92</td>
</tr>
<tr>
<td>GEP Class 2*</td>
<td>6.13</td>
</tr>
</tbody>
</table>

* No MSS events occurred in Class 1A group therefore MSS multivariate analysis performed on binary class without subclass.

Gastman et al. JAAD 2018
31-GEP identifies patients at **HIGH RISK** of recurrence and distant metastasis in Stage I and IIA (NCCN – Low Risk) patients

<table>
<thead>
<tr>
<th>GEP Result</th>
<th>5-year RFS</th>
<th>Event Rate (n)</th>
<th>5-year DMFS</th>
<th>Event Rate (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A (n=259)</td>
<td>96%</td>
<td>5% (14)</td>
<td>97%</td>
<td>4% (10)</td>
</tr>
<tr>
<td>1B (n=52)</td>
<td>88%</td>
<td>12% (6)</td>
<td>88%</td>
<td>12% (6)</td>
</tr>
<tr>
<td>2A (n=36)</td>
<td>81%</td>
<td>19% (7)</td>
<td>86%</td>
<td>14% (5)</td>
</tr>
<tr>
<td>2B (n=46)</td>
<td>61%</td>
<td>43% (20)</td>
<td>76%</td>
<td>28% (13)</td>
</tr>
</tbody>
</table>
Multivariate analysis shows GEP adds prognostic information independent from staging factors

| Cox Multivariate Analysis | RFS | | DMFS | | MSS |
|--------------------------|-----|-----|-----|-----|-----|-----|
|                          | HR  | 95% CI | P-value | HR  | 95% CI | P-value | HR  | 95% CI | P-value |
| Breslow depth            | 1.21 | 1.12-1.3 | <0.0001 | 1.19 | 1.09-1.29 | <0.0001 | 1.16 | 1-1.34 | 0.05   |
| Mitotic rate             | 1.01 | 0.99-1.03 | 0.18   | 1.01 | 0.99-1.03 | 0.24   | 0.97 | 0.92-1.03 | 0.34 |
| Ulceration               | 1.1  | 0.75-1.59 | 0.64   | 1.57 | 1.02-2.43 | 0.04   | 0.77 | 0.38-1.57 | 0.47 |
| Positive node            | 2.45 | 1.74-3.46 | <0.0001 | 3.02 | 2-4.57 | <0.0001 | 3.81 | 1.83-7.96 | 0.0003 |
| GEP Class 1B             | 1.13 | 0.56-2.29 | 0.73   | 1.35 | 0.58-3.15 | 0.48   | 4.37 | 0.84-22.72 | 0.08 |
| GEP Class 2A             | 1.48 | 0.77-2.84 | 0.24   | 1.53 | 0.68-3.43 | 0.30   | 2.52 | 0.42-15.2 | 0.21 |
| GEP Class 2B             | 2.92 | 1.7-5   | <0.0001 | 2.89 | 1.49-5.62 | 0.002  | 9.02 | 2.02-40.24 | 0.004 |
melanoma-specific survival by stage

31-GEP validation cohort with AJCC v8 staging

<table>
<thead>
<tr>
<th>Stage (n)</th>
<th>5-year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (344)</td>
<td>98.5%</td>
</tr>
<tr>
<td>II (138)</td>
<td>90.7%</td>
</tr>
<tr>
<td>III (208)</td>
<td>75.8%</td>
</tr>
</tbody>
</table>

AJCC 8th Edition cohort

<table>
<thead>
<tr>
<th>Stage (n)</th>
<th>5-year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (10974)</td>
<td>98%</td>
</tr>
<tr>
<td>II (4717)</td>
<td>90%</td>
</tr>
<tr>
<td>III (4622)</td>
<td>77%</td>
</tr>
</tbody>
</table>
Prospective studies have confirmed that the 31-GEP test is a robust and independent prognostic factor.

**Validation & Performance Studies**

**Prospective Studies**

**Clinical Impact Studies**

- Multicenter registry
  - *J Hematol Oncol*
  - 2017

- Hsueh et al. ASCO 2016

- Greenhaw et al. *Dermatol Surg*

Combined **702** patients across studies
Patients with GEP Class 2 test result were 22 times more likely to develop metastatic disease

- Class 2 patients were **22 times more likely to develop metastatic disease**
- 76.9% of metastatic patients were correctly identified as high risk
- NPV of ~99% provides confidence in low risk of metastasis and mortality for Class 1 patients

<table>
<thead>
<tr>
<th></th>
<th>Metastatic Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GEP</strong></td>
<td>No</td>
</tr>
<tr>
<td>Class 1</td>
<td>211</td>
</tr>
<tr>
<td>Class 2</td>
<td>32</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>243</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>0.769</td>
</tr>
<tr>
<td></td>
<td>0.460-0.938</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>0.868</td>
</tr>
<tr>
<td></td>
<td>0.818-0.907</td>
</tr>
<tr>
<td><strong>Negative Predictive Value</strong></td>
<td>0.986</td>
</tr>
<tr>
<td><strong>Positive Predictive Value</strong></td>
<td>0.238</td>
</tr>
<tr>
<td><strong>Odds ratio</strong></td>
<td>22.0</td>
</tr>
<tr>
<td></td>
<td>5.7-84.2</td>
</tr>
</tbody>
</table>
31-GEP identifies patients at high risk of recurrence and distant metastasis in patients with thin (≤1mm) tumors

**GEP Class**

<table>
<thead>
<tr>
<th>GEP Class</th>
<th>5-year RFS (95% CI)</th>
<th>Event Rate (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A (n=217)</td>
<td>97% (94-99%)</td>
<td>4% (9)</td>
</tr>
<tr>
<td>1B (n=34)</td>
<td>91% (82-100%)</td>
<td>9% (3)</td>
</tr>
<tr>
<td>2A (n=15)</td>
<td>100% (100-100%)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>2B (n=15)</td>
<td>65% (44-95%)</td>
<td>40% (6)</td>
</tr>
</tbody>
</table>

**Cox Multivariate Analysis**

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breslow depth</td>
<td>0.6</td>
<td>0.01-32.81</td>
<td>0.80</td>
</tr>
<tr>
<td>Mitotic rate</td>
<td>1.03</td>
<td>0.81-1.3</td>
<td>0.83</td>
</tr>
<tr>
<td>Ulceration</td>
<td>2.26</td>
<td>0.41-12.56</td>
<td>0.35</td>
</tr>
<tr>
<td>Positive node</td>
<td>4.16</td>
<td>0.79-21.82</td>
<td>0.09</td>
</tr>
<tr>
<td>GEP Class 1B</td>
<td>0.52</td>
<td>0.05-5.23</td>
<td>0.58</td>
</tr>
<tr>
<td>GEP Class 2A</td>
<td>0</td>
<td>0-inf</td>
<td>1.0</td>
</tr>
<tr>
<td>GEP Class 2B</td>
<td>9.34</td>
<td>2.03-42.97</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Validation and clinical impact studies: n >2,600 patients

Validation & Performance Studies
- Gastman et al. JAAD 2018 - NEW
- Vetto et al. AAD 2018 - NEW
- Zager et al. BMC Cancer 2018
- Gerami et al. CCR 2015
- Gerami et al. JAAD 2015
- Cook et al. Diagn Pathol 2018

Prospective Studies
- Hsueh et al. J Hematol Oncol 2017
- Renzetti et al. SSO 2017
- Hsueh et al. ASCO 2016

Clinical Impact Studies
- Dillon et al. SKIN 2018 - NEW
- Schuitevoerder et al. J Drugs Dermatol 2018 - NEW
- Hyams et al. WCD 2018 - NEW
- Svoboda et al. J Drugs Dermatol 2018 - NEW
- Farberg et al. J Drugs Dermatol 2017
- Berger et al. CMRO 2016
T1a / Stage IA melanoma patient

• 34-year-old female with melanoma on arm
  • Breslow depth: 0.6mm, no ulceration (T1a), mitotic rate <1/mm²
  • AJCC Stage IA
31-GEP ordered by Dermatology:
  • Class 2B result
Clinical management of patient with Class 2B tumor

- Referred to Medical Oncologist for high-intensity surveillance
  - CT scan - clear
  - CT scan six months later - biopsy proven oligomet to the lung, BRAF negative
- Started on combination ipilimumab/nivolumab, and doing well (clear scans) after 6 months
Risk of recurrence drives management decisions for melanoma patients – including informing SLNB

Management of Stage I-III melanoma patients involves making decisions on:

• Frequency of follow-up
• Frequency and modality of surveillance imaging
• Referral to Surgical Oncology
• Sentinel Lymph Node Biopsy
• Referral to Medical Oncology
• Adjuvant therapy

NCCN guidelines recognize that a patient’s individual risk of recurrence should drive management decisions

NCCN guidelines also recognize that a patient’s individual risk of SLN positivity (recurrence to the SLN) drives SLN biopsy recommendations
Consistent risk of recurrence results in 6 studies \( n > 1,300 \)

Gerami et al. *Clin Cancer Res* 2015


Zager et al. *BMC Cancer* 2018

Greenhaw et al. *Dermatol Surg* 2018

Multicenter registry *J Hematol Oncol* 2017

Hsueh et al. *ASCO* 2016

Archival

Prospective

% Disease Free

% Recurrence Free

% Recurrence Free

% Recurrence Free

Class 1

Class 1

Class 1

Class 1

Class 2

Class 2

Class 2

Class 2

\( p < 0.0001 \)

\( p < 0.0001 \)

\( p < 0.0001 \)

\( p < 0.0001 \)
31-GEP provides robust separation of recurrence risk in a second prospective, independent study in a dermatology practice

5-year recurrence-free survival probability:
- Class 1 = 93% (CI: 83%-100%)
- Class 2 = 69% (CI: 52%-90%)

Post-study protocol uses 31-GEP result to drive management decisions:
- **Class 1** - clinical skin and nodal exams every 6 months for 2 years, then yearly thereafter
- **Class 2** - clinical skin and nodal exams every 3 months for 2 years, then every 6 months for 3 years, then yearly thereafter
31-GEP subclass can predict SLNB positivity risk for patients with T1-T2 tumors and inform SLNB guidance

SLN+ probability in T1-T2 patients:
- Is below the 5% threshold established by guidelines in those ≥55 years old with a Class 1A result
- Is above the 10% threshold established by guidelines in all age groups with a Class 2B result

### 31-GEP result

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Probability</th>
<th>NCCN Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;55 years</td>
<td>7.6%</td>
<td>Discuss and Offer</td>
</tr>
<tr>
<td>55-64 years</td>
<td>4.9%</td>
<td>Discuss and Consider</td>
</tr>
<tr>
<td>≥65 years</td>
<td>1.6%</td>
<td>Do not Recommend</td>
</tr>
</tbody>
</table>

### NCCN Recommendations for SLNB (v3.2018)

- Discuss and Offer
- Discuss and Consider
- Do not Recommend

Thresholds based on NCCN Guidelines (v3.2018) n=1,065
For patients aged ≥55 years, Class 1A patients are at a very low risk of recurrence while Class 2B show higher risk.
Patients with either T1 or T2 tumors who have a Class 1A result and are ≥55 years of age show SLN positivity rates <5%.

<table>
<thead>
<tr>
<th>T-stage</th>
<th>SLN positivity rate in Class 1A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with Class 1A Result (n)</td>
</tr>
<tr>
<td>Age &lt;55</td>
<td>T1 219 5.6%</td>
</tr>
<tr>
<td></td>
<td>T2 151 12%</td>
</tr>
<tr>
<td>Age ≥55</td>
<td>T1 394 1.8%</td>
</tr>
<tr>
<td></td>
<td>T2 301 4.9%</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>T1 255 0.9%</td>
</tr>
<tr>
<td></td>
<td>T2 193 3.0%</td>
</tr>
</tbody>
</table>
New clinical use for the 31-GEP test to inform SLNB decision in common patient type

• SLNB eligible patients with T1-T2 tumors
  • Identify patients who have a <5% likelihood of a positive SLN (Class 1A) and thus no recommendation for SLNB based on current clinical thresholds
    • Low-risk Class 1 patients can avoid SLNB and associated surgical and anesthesia risk, as well as intensive follow up and exposure to radiation from imaging procedures
  • Identify patients who have a >10% likelihood of a positive SLN (Class 2B) and thus should be offered a SLNB according to NCCN guidelines
    • High-risk Class 2 patients have improved guidance to perform SLNB

Enrichment for SLN positive patients in the group that undergoes SLNB allows for better allocation of healthcare resources for those who have a higher likelihood of benefiting from targeted and immunotherapeutic agents in the adjuvant setting
T2a / Stage IIA melanoma patient case

- 52 year old male with melanoma on right lower leg presented to general surgeon for discussion of SLNB
  - Breslow depth: 1.2mm, no ulceration (T2a), mitotic rate <1/mm²
  - SLN of right groin – negative
  - AJCC Stage IIA
- 31-GEP test ordered after SLNB
  - Class 2B result

Clinical management of patient with Class 2B tumor

- Patient sent to medical oncology for high intensity surveillance and clinical trial consideration
  - Initial PET/CT scan - intense, abnormal uptake on the left lateral deep cervical node
  - Biopsy & removal of left lateral deep cervical nodes
    - Now Stage IV due to metastatic disease in distant nodes
  - Offered immunotherapy for low-burden metastatic disease.
Addition of the 31-GEP test to staging consistently impacts clinical management decisions for one of every two patients tested

- Four consecutive clinical impact studies have shown 47-53% change in management
- Management changes include:
  - Clinical visit frequency
  - Imaging and labs
  - Referrals
  - Sentinel lymph node biopsy guidance

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th># of Patients</th>
<th>% Change in Management</th>
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</thead>
<tbody>
<tr>
<td>Berger et al. CMRO 2016</td>
<td>Prospectively tested patients. Retrospective chart review.</td>
<td>156</td>
<td>53%</td>
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<tr>
<td>Dillon et al. SKIN J Cutan Med 2018</td>
<td>Prospective documentation of pre and post test plans</td>
<td>247</td>
<td>49%</td>
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<tr>
<td>Farberg et al. J Drugs Derm 2017</td>
<td>Physician survey</td>
<td>n/a</td>
<td>47-50%</td>
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<tr>
<td>Schuitevoerder et al. J Drugs Derm 2018</td>
<td>Modeling in prospective cohort</td>
<td>91</td>
<td>52%</td>
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</table>
Prospective multicenter clinical utility study shows impact in management decisions similar to previous studies

- 49% of tested patients had a change in clinical management.
- 91% of decreases in care provided to low-risk Class 1 patients and 72% of increases in care provided to high-risk Class 2 patients.
- Informs appropriate clinical management and patient care, with similar changes to previously published studies.¹-³


Dillon et al. SKIN: J Cutan Med 2018
### Earlier identification of metastasis can maximize treatment success

<table>
<thead>
<tr>
<th>Author</th>
<th>Therapy Investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribas et al. 2016</td>
<td>Pembrolizumab</td>
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<tr>
<td>Joseph et al. 2018</td>
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<tr>
<td>Lyle et al. 2014</td>
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<td>Huang et al. 2017</td>
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<td>Long et al. 2016, 2017 (2)</td>
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<tr>
<td>Schadendorf et al. 2017</td>
<td>Dabrafenib + trametinib</td>
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<td>Menzies et al. 2014</td>
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<td>Kaufman et al. 2015</td>
<td>T-VEC</td>
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<tr>
<td>Steinman et al. 2014</td>
<td>Isolated limb infusion</td>
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<tr>
<td>Nishino et al. 2014</td>
<td>Ipilimumab + bevacizumab</td>
</tr>
</tbody>
</table>

- Treatment of patients with lower tumor burden can result in better response rates and/or improved progression free survival (PFS) and overall survival (OS)

**Pembrolizumab**

- Better objective response rate shown with lower tumor burden (Ribas et al. 2016)
- Baseline tumor size was the strongest independent prognostic factor (Joseph et al. 2018)

**Dabrafenib + trametinib**

- Best response and PFS rates seen in patient with lower tumor burden and normal LDH (Schadendorf et al. 2017)
Clinical follow up and imaging allow detection of nodal and distant recurrences with impact on survival

- Imaging can identify >80% of metastasis while asymptomatic\(^1\)\(^-\)\(^3\)

- A substantial proportion of nodal recurrences are identified during follow up physician exams\(^1\)\(^-\)\(^3\)

- Earlier detection of recurrences has a significant survival benefit for Stage I-III patients, even accounting for lead-time bias\(^4\)\(^-\)\(^5\)

Proportion of **distant metastasis** detected by imaging:

- **84%**
  - Podlipnick et al. (2016)
  - Prospective study, n=290

- **75%**
  - Park et al. (2017)
  - 4 prospective NCI studies, n=466

- **96%**
  - Livingstone et al. (2015)
  - Prospective, multi-center study, n=668

3. Livingstone et al. 2015. *Eur J Cancer*
Use of GEP Test to Determine SLNB Eligibility in ≥65 yo

Background

• Older age is associated with a poor prognosis, but these patients show low rates of sentinel lymph node (SLN) biopsy positivity.

• The 31-gene expression profile (GEP) test determines a CM patient’s risk for metastatic disease, classifying patients into low (Class 1) or high (Class 2) risk groups.

• Patients with a Class 1 tumor profile also have low rates of SLN positivity.
Validation of Thresholds for SLNB Prediction

Retrospective Cohort
Stage I-IV (n=946)
- Probability score: ≤0.5 (Class 1)
- Breslow Thickness: ≤2.0mm
- Age: ≥65 years
- Factors not contributing: ulceration, mitoses

Validation Cohort 1:
Prospective, Multicenter Studies
(n=584)

Validation Cohort 2:
Independent, Academic Institutional, Multicenter, Prospective Study
(n=837)

Combined Cohort:
Enables analysis by age (n=1,421)
Use of GEP Test to Determine SLNB Eligibility in ≥65 yo

Methods

- Bioinformatics modeling was performed on a retrospective cohort (n=946) to identify a population with a positive SLNB rate below 5%.
  - Neural networks, tree-based models, support vector machine, self organizing maps, radial basis machine
  - No other model outperformed the current GEP algorithm in combination with Breslow thickness and age

- Outcome data was derived from the retrospective cohort

Fleming, M.D 2017 Abstract, Society of Melanoma Research, Brisbane, Australia.
Use of GEP Test to Determine SLNB Eligibility in ≥65 yo

Results

• Patients ≥65 years old with Class 1 T1-T2 tumor, had a SLN positive rate of 2% (NPV=98%).

• The SLN positivity rate was enriched from 9% using current SLNB criteria to 15% if this group of patients was spared the procedure.

• The expected 5-year melanoma specific survival (MSS) rate for T1-T2 Class 1 patients based on the retrospective dataset was 98% with overall survival (OS) of 94% and distant metastasis free survival (DMFS) of 92%.
Combined Cohort Analysis by Age and GEP Class

NCCN Cut-Points for SLNB (2.2018)

Discuss and Offer

Discuss and Consider

Do Not perform

*Per NCCN Guidelines (v2.2018)
Combined Cohort Analysis by Age and GEP Subclass

**NCCN Cut-Points for SLNB (2.2018)**

- **Discuss and Offer**
- **Discuss and Consider**
- **Do Not perform**

### All Patients

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### SLNB Eligible* or Assessed

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</table>

*Per NCCN Guidelines (v2.2018)
What happens to a T1-T2 patient if you eliminate SLNB with a Class 1A result?

<table>
<thead>
<tr>
<th>Clinical T1/T2 Melanoma</th>
<th>31 Gene GEP</th>
<th>Class 1A</th>
<th>No SLNB</th>
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</thead>
<tbody>
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<td>Class 1B, 2A, 2B</td>
<td>SLN B</td>
<td>SLN Neg</td>
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<td></td>
<td>SLN Pos</td>
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</table>

5-year survival rates

<table>
<thead>
<tr>
<th></th>
<th>MSS</th>
<th>OS</th>
<th>DMFS</th>
<th>RFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1A No SLNB</td>
<td>99.6%</td>
<td>98.2%</td>
<td>95.3%</td>
<td>93.5%</td>
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<tr>
<td>SLN Neg</td>
<td>94.1%</td>
<td>91.7%</td>
<td>85.9%</td>
<td>82.6%</td>
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<tr>
<td>SLN Pos</td>
<td>83.1%</td>
<td>63.8%</td>
<td>61.0%</td>
<td>55.0%</td>
</tr>
</tbody>
</table>

N= 690 with 5 years follow up (or recurrent event)
Use of GEP Test to Determine SLNB Eligibility in >65 yo

Conclusions

• The 31-gene expression profile can identify a patient population with \( \leq 5\% \) likelihood of a positive SLN
  • \( \geq 65 \) years-old, T1-T2, Class 1A shows a 2\% SLN positive rate

• Use of the test could potentially reduce the rate of SLN biopsy by up to 44\% without affecting patient outcomes

• In the \( \geq 65 \) yo population, the rate of SLN positives is increased (from 9\% to 15\%) in the group of patients who would be recommended for SLNB