Update on gene expression profiling tests for melanoma

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Summer AAD S001 – Advances in melanoma
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Declarations

• I will discuss three commercial products
  ❖ Pigmented Lesion Assay™ (Dermtech)
  ❖ myPath® Melanoma test (Myriad Genetics)
  ❖ Decision Dx Melanoma™ test (Castle Biosciences)

• I have no financial interest in any of these products or companies

• I am not a paid consultant or speaker for any of these companies
When confronted with a pigmented lesion...

- Do I need to do a biopsy?
  
  Pigmented Lesion Assay™
  (Dermtech)
  Diagnostic 2-GEP

- Is it a nevus or melanoma?
  
  myPath® Melanoma
  (Myriad Genetics)
  Diagnostic 23-GEP

- Is this melanoma high-risk?
  
  Decision Dx Melanoma™
  (Castle Biosciences)
  Prognostic 31-GEP

GEP testing: defining “high-risk” on a molecular level
Diagnostic uncertainty: nevus or melanoma?

Nevus
- Asymmetric architecture
- Pagetoid melanocytes
- Mitoses
- Spitzoid features
- Outcome: No recurrence or metastasis
- Treatment: None

Melanoma
- Value of molecular test: improve diagnostic certainty and prediction of biologic behavior
- Outcome: Metastasis, death
- Treatment: Wide local excision, SLNB

Re-excision
- Diagnostic uncertainty
- Risk of over-treatment
Prognostic uncertainty in melanoma

- 3-5% of patients with minimally invasive melanoma will ultimately develop distant metastatic disease  
  Gershenwald, *CA Cancer J Clin* 2017

- No reliable predictive factor to identify these patients, who represent 20-30% of melanoma deaths  
  Criscione, *JID* 2010; Whiteman, *JID* 2015

- SLNB: identifies (5-7%) patients with nodal metastasis from thin melanoma  

- Value of molecular **prognostic test** to improve staging accuracy for patients who could receive more frequent follow-up, imaging, and/or adjuvant therapy
Diagnostic 2-GEP (Pigmented Lesion Assay™)

- Based on gene expression from stratum corneum
- Non-invasively removed from lesion by tape-stripping
- Cellular RNA is extracted from the adhesive patch, followed by quantitative PCR
- Not for mucous membranes, palms, soles, nails, or ulcerated or bleeding lesions
- Kit containing the adhesive patches and mailing supplies
- Results returned via fax or online portal in 2-3 days
- Cost: attempt to bill insurance, $50 if not covered ($249 if self-pay), no charge for technical failures or charge for >3 lesions tested on same day

http://dermtech.com
Diagnostic 2-GEP (cont’d)

• Narrowed classifier from 17 to 2 genes: **97% sensitivity, 70% specificity** Gerami, *JAAD* 2014
  LINC00518 (a non-coding long RNA) Preferentially Expressed Antigen in Melanoma (PRAME)

• Aberrant expression of both LINC00518 and PRAME: high risk
  only one gene: moderate risk
  neither gene: low risk

• 2nd study: 398 pigmented lesions Gerami, *JAAD* 2017
  91% sensitivity, 69% specificity

• 381 lesions: 330 PLA-, bx deferred; 51 PLA+, bx done (37% melanoma) Ferris, *Melanoma Res* 2018

• 2309 lesions: **>99% negative predictive value** Ferris, *Dermatol Online J* 2019

• May not be practical to have patient return for biopsy 3-5 days later
37-y/o male with new lesion on the back

- Baseline photograph
- At annual f/u exam

Peri-follicular hypopigmentation

Unrelated new nevus

2-GEP PLA assay

Linc– PRAME– (low-risk)

Observe

- Utility: Avoid biopsy when likely benign lesion
- No indication: If the decision to biopsy has been made
64-y/o male with h/o 7 melanomas

- 2/8/19 – New patient visit: lots of atypical lesions, mole mapping done
- 5/3/19 – 1st f/u visit: 1 changing lesion: MM 0.6 mm; 1 atypical unchanging lesion: MIS
- 5/22/19 – tape-stripping for 2-GEP of 10 most clinically atypical remaining lesions

Melanoma, 0.3 mm
- Linc+ PRAME–

Melanoma in situ
- Linc− PRAME–
- Linc+ PRAME+
- Linc+ PRAME+
- Linc− PRAME–
- Linc− PRAME–
- Linc− PRAME–
- Linc− PRAME–

Another utility: able to screen multiple lesions, relatively inexpensive
When confronted with a pigmented lesion...

- Do I need to do a biopsy?
- Is it a nevus or melanoma?
- Is this melanoma high-risk?

myPath® Melanoma
(Myriad Genetics)
Diagnostic 23-GEP

skinva.com
Diagnostic 23-GEP test (myPath® Melanoma)

- Developed as an adjunct to histopathology for lesions which cannot be confidently identified by histology alone

- RNA isolated from FFPE slides
  - 14 genes (cell differentiation, immune response, cell signaling)
  - 9 control (housekeeping) genes

- Each case requires H&E-stained slide and several unstained slides

- Cost: $1950 (attempt to bill insurance first)

- Scores are available after 5-7 days via an online portal

- Melanoma diagnostic score (MDS):
  - likely malignant, benign, or indeterminate

https://mypathmelanoma.com/
Melanocytic lesions (benign or malignant) sensitivity and specificity >90% validated in cohorts of 437 and 1400 samples Clarke, *J Cutan Pathol* 2015; Clarke, *Cancer* 2017

Correlation with clinical outcomes Ko, *Cancer Epidemiol Biomarkers Prev* 2017
99 melanomas with proven distant mets
83 nevi >5 years f/u (median 6.2 years) with no adverse events sensitivity: 93.8%; specificity: 96.2%

MDS increased definitive diagnoses made by dermatopathologists and reduced indeterminate diagnoses by 42% Cockerell, *Medicine* 2016; Cockerell, *Per Med* 2017

Utility: when there is diagnostic uncertainty (atypical nevus vs. melanoma)

No indication: if the histologic diagnosis is clear
When confronted with a pigmented lesion...

- Do I need to do a biopsy?
- Is it a nevus or melanoma?
- Is this melanoma high-risk?

**Decision Dx Melanoma™**
(Castle Biosciences)
Prognostic 31-GEP

skinva.com
Prognostic 31-GEP test (Decision Dx-Melanoma™)

- Designed to identify early-stage primary melanomas with high risk of metastasis
  - Built on prior data and prognostic test for uveal melanoma
  - RNA isolated from FFPE material: 31-gene panel (28 signature, 3 control)
  - Differential expression in “low risk” and “high risk” primary melanoma tumors
  - GEP result: either Class 1 (low risk) or Class 2 (high risk)
- Order form downloaded from company’s website (http://castlebiosciences.com)
- Archival tissue with sufficient tumor remaining to cut multiple slides required
- Cost: $8000, bill insurance and accept any payment; assistance program if uninsured
- Turn-around time: 7-10 days once receive tissue
Retrospective validation of the 31-GEP test

- 690 pooled melanoma cases (stages I-III) with either metastatic event or >5 years of follow-up without metastasis from 18 centers

Zager, BMC Cancer 2018; Gastman, JAAD 2019

Class 1A

Class 1B

Class 2A

Class 2B

Multivariate HR for metastasis

- Breslow depth: 1.19 (1.09-1.29)
- Ulceration: 1.57 (1.02-2.43)
- Positive SLN: 3.02 (2.0-4.57)
- GEP Class 1B: 1.35 (0.58-3.15)
- GEP Class 2A: 1.53 (0.68-3.43)
- GEP Class 2B: 2.89 (1.49-5.62)

259 patients with negative SLN
Recent prospective studies of the 31-GEP test

- 159 prospectively tested patients (113 were T1/T2)  
  Keller, *Cancer Med* 2019
- 86 prospectively tested T1/T2 patients  
  Podlipnik, *J Eur Acad Dermatol Venereol* 2019

### multivariate HR for metastasis

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<thead>
<tr>
<th>Factor</th>
<th>HR</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Breslow depth</td>
<td>1.2</td>
<td>(1.0-1.4)</td>
</tr>
<tr>
<td>Ulceration</td>
<td>2.5</td>
<td>(0.7-8.5)</td>
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<tr>
<td>Positive SLN</td>
<td>3.8</td>
<td>(1.2-11.3)</td>
</tr>
<tr>
<td>GEP Class</td>
<td>19</td>
<td>(2.1-170)</td>
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### multivariate HR for recurrence

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<thead>
<tr>
<th>Factor</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age onset (&gt;50)</td>
<td>3.7</td>
<td>(0.43-486)</td>
</tr>
<tr>
<td>AJCC stage (IIB,C)</td>
<td>1.52</td>
<td>(0.36-8.77)</td>
</tr>
<tr>
<td>GEP (Class 2)</td>
<td>18.82</td>
<td>(1.81-2,549)</td>
</tr>
</tbody>
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- 1421 prospectively-tested T1/T2 patients, most undergoing SLNB, 26 centers  
  Vetto, *Future Oncol* 2019

SLN positivity rates:

- Class 1A, age 55-64: 4.9%
- Class 1A, age 65+: 1.6%

Given threshold of 5% positivity risk for considering SLNB, Class IA patients age 55+ could be spared SLNB
Current use of GEP tests for melanoma

• Use is increasingly prevalent, number of tests processed in 2018: *
  2-GEP PLA tests: 14,000
  23-GEP myPath® tests: 3000
  31-GEP Decision Dx-Melanoma™ tests: 12,000

• May represent up to 10% of all invasive melanomas are GEP-tested!

• Insurance coverage by Centers for Medicare and Medicaid Services:
  23-GEP myPath® (if ordered by dermatopathologists)
  31-GEP Decision Dx-Melanoma™ (patients over age 65, T1a with adverse features, T1b, T2)

* Personal communications from Stewart Lester (DermTech), Loren Clarke (Myriad), Bob Cook (Castle)
GEP tests not recommended by NCCN or AAD

Routine (baseline) prognostic GEP testing of primary cutaneous melanomas **not recommended** outside of a clinical study (or trial)


“...inconsistency of results across studies aimed at defining the most predictive gene sets for melanoma.”

Referring specifically to the 31-GEP test:

“Not been directly evaluated in the context of all known prognostic characteristics of localized melanoma”

“Its independent prognostic value has yet to be confirmed in a large population of patients with average to low risk melanoma”

AAD Melanoma Guidelines  Swetter, JAAD 2019

“Routine molecular testing...for prognostication...discouraged until better use criteria are defined.”
What are pigmented lesion experts doing?

- Jotform-based survey of 50 Pigmented Lesion Subcommittee members of the national Melanoma Prevention Working Group and additional pigmented lesion clinic directors

- 42/50 (84%) responses; Proportion ever ordering GEP test:
  - 2-GEP PLA™: 21%; 23-GEP myPath®: 21%; 31-GEP Decision Dx-Melanoma™: 29%

- GEP tests most commonly were ordered less than once per month

- No correlation between test usage and years experience, or percent of practice devoted to pigmented lesions

- Most respondents (63%) ordering tests reported that results impacted patient care:
  - myPath®: decisions to re-excise or excision margin determination
  - PLA™: to avoid or justify biopsy of a lesion
  - Decision Dx-Melanoma™: to justify enhanced imaging surveillance, and affected recommendations for SLNB and adjuvant therapy

- Reasons respondents not ordering tests: perceived lack of utility, need for further validation, not advocated by guidelines, potential cost

Varedi, JAAD (under review)
Unknowns for prognostic GEP

• Which patients/tumors to test
• Whether GEP testing can replace established staging parameters (e.g. SLNB)
• Whether GEP testing be used to predict SLNB positivity
• Whether GEP testing should be used in combination with other staging parameters
• What actions (if any) should be taken based on GEP test results
  No FDA-approved therapies for a patient with a “high-risk” GEP result
• Whether GEP test results can be used to predict benefit from enhanced surveillance
  If so, which tumor stage(s)?
• Whether GEP test results can be used to predict benefit from adjuvant therapy
  If so, which tumor stage(s)?

The solution: carefully designed prospective randomized clinical trials
GEP summit meeting at SMR

Purpose: multi-disciplinary team to discuss/plan future GEP trial

Summit meeting organizers: Doug Grossman and Sancy Leachman
doug.grossman@hci.utah.edu          leachmas@ohsu.edu

Please contact us if interested in participating!