New molecular diagnostic and prognostic tests for melanoma

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Summer AAD S011 – Advances in melanoma
July 28, 2018
Declarations

• I will discuss three commercial products
  - Pigmented lesion assay (PLA, Dermtech)
  - myPath® Melanoma (Myriad Genetics)
  - Gene expression profile (GEP, Castle Biosciences)

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

• I am not a consultant or speaker for any of these companies

• I have not (yet) personally ordered any of these tests for my patients

• I have no conflicts of interest !!!
When confronted with a pigmented lesion...

- Do I need to do a biopsy?
  Pigmented lesion assay (PLA, Dermtech)

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

- Is this thin melanoma high-risk?
  Gene expression profile (GEP, Castle Biosciences)
Dermtech’s pigmented lesion assay (PLA)

- 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 in 3-5 days
- Cost: attempt to bill insurance, $50 if not covered ($249 if self-pay)

http://dermtech.com
Non-invasive PLA test (cont’d)

• Initial study: differentially expressed genes in melanomas and nevi
  narrowed panel of 312 genes to 17 genes
discriminated melanomas from nevi: 100% sensitivity, 88% specificity
  Wachsman, BJD 2011

• Limiting the classifier to two 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
  91% sensitivity, 69% specificity
  Gerami, JAAD 2017

• PLA test improved biopsy decision-making among dermatologists
  Ferris, JAMA Dermatol 2017

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

- When there is **clinical uncertainty**: nevus vs. melanoma
- No indication:
  - If the decision to biopsy has been made
- Advantages:
  - **High sensitivity** (>90%)
  - Non-invasive
  - **Avoid biopsy in cosmetically-sensitive areas**
  - Relatively inexpensive
  - Able to screen multiple lesions
- Disadvantages:
  - **Moderate specificity** (70%)
  - **May not be practical to have patient return for biopsy 3-5 days later**
When confronted with a pigmented lesion...

- Do I need to do a biopsy?
- Is it a nevus or melanoma?
  myPath® Melanoma (Myriad Genetics)
- Is this thin melanoma high-risk?
Diagnostic uncertainty: nevus or melanoma?

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

**Melanoma**
- Diagnostic uncertainty
- Risk of over-treatment
- Treatment: Re-excision, Wide local excision, SLNB
- Outcome: Metastasis, death

Diagnostic certainty
Myriad Genetics’ myPath® Melanoma test

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

• RNA isolated from FFPE slides

• Training cohort of 464 nevi and melanomas
  23 genes: cell differentiation, immune response and cell signaling
  9 control genes

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

• Melanocytic lesions (benign or malignant)
  sensitivity and specificity ~90%
  validated in a second cohort of 437 samples

Clarke, J Cutan Pathol 2015
myPath® Melanoma test (cont’d)

- Each case requires an 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
- Reproducibility of the assay  
  - Warf, Biomark Med 2015
- Subsequent validation study: sensitivities and specificities of >90%  
  - 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 affected treatment decisions made by dermatologists  
  - Cockerell, Medicine 2016; Cockerell, Per Med 2017
Utility of myPath® Melanoma test

• When there is diagnostic uncertainty (atypical nevus vs. melanoma)

• No indication:
   If the histologic diagnosis is clear

• Advantages:
   May reduce indeterminate diagnoses
   High sensitivity and specificity

• Potential applications (but no data yet):
   To determine whether dysplastic or Spitz nevi should be re-excised
   To guide margins for atypical nevus re-excisions
When confronted with a pigmented lesion...

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

Gene expression profile (GEP, Castle Biosciences)
Prognostic tests for thin melanoma

- 3-5% of patients with minimally invasive stage IA disease 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: Wright, Arch Surg 2008; Venna, JAAD 2013; Gershenwald, 2017 identifies (5-7%) patients with nodal metastasis from thin melanoma

- Value of additional prognostic test to improve staging accuracy for patients who could receive closer follow-up and/or adjuvant therapy
Decision Dx-Melanoma test (Castle Biosciences)

- Designed to identify early-stage primary melanomas with high risk of metastasis
- Prior studies: gene expression (i.e. gene signatures) associated with melanoma tumor progression and metastasis  
- Gene expression profile (GEP) test  
  Gerami, *Clin Cancer Res* 2015
  Built on prior data and Castle 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
  algorithm: GEP classifies tumor as either Class 1 (low risk) or Class 2 (high risk)
- Order form downloaded from company’s website ([http://castlebiosciences.com](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
Clinical validation studies of the GEP test

• Initial study: 78 cases of AJCC-classified stage I-II melanoma associated with either metastatic event or >5 years of follow-up without metastasis
  Gerami, Clin Cancer Res 2015
  overall survival for Class 1: 98-100%, for Class 2: 37-68%
  164 stage I/IIA cases: 90% without mets were Class 1, 80% with mets were Class 2

• 2nd study: GEP test in 217 patients prior to SLNB
  Gerami, JAAD 2015

Predictive values for distant mets

<table>
<thead>
<tr>
<th></th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>SLNB</td>
<td>55 (42-68)</td>
<td>67 (59-74)</td>
</tr>
<tr>
<td>GEP</td>
<td>50 (42-59)</td>
<td>82 (71-89)</td>
</tr>
</tbody>
</table>

**Multivariate HR for distant mets**

<table>
<thead>
<tr>
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<th>HR (95% CI)</th>
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<tr>
<td>SLNB+</td>
<td>2.1 (1.3-3.3)</td>
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NS
Clinical validation studies of the GEP test

- 3rd study: further improve prognostic accuracy by combining GEP test with AJCC Outcome Prediction Tool (http://melanomaprognosis.net) Ferris, JAAD 2017

- Interim analysis of GEP test in 322 patients in trial registries Hsueh, J Hematol Oncol 2017
  thickness, mitotic rate, and GEP class significantly predicted recurrence
  only tumor thickness significantly predicted distant mets and overall survival
  median f/u time only 1.5 years for event-free patients

- Multi-center study, 523 cases with metastasis or ≥5 years event-free Zager, BMC Cancer 2018

<table>
<thead>
<tr>
<th>multivariate HR for metastasis</th>
<th>RFS n=314</th>
<th>RFS n=225</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitotic rate (≥1/mm²)</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Ulceration</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Breslow depth</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>GEP Class 2</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>SLNB+</td>
<td>3.0</td>
<td></td>
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</tbody>
</table>
## Case scenarios – applications of GEP test?

<table>
<thead>
<tr>
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<th>2018 NCCN</th>
<th>GEP Class 1</th>
<th>GEP Class 2</th>
</tr>
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<tbody>
<tr>
<td><strong>Stage IA patient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommend SNLB</td>
<td>No</td>
<td>No</td>
<td>?</td>
</tr>
<tr>
<td>Imaging surveillance</td>
<td>No</td>
<td>No</td>
<td>?</td>
</tr>
<tr>
<td><strong>Stage IIC patient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommend SLNB</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>Regional imaging (SLNB-)</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Stage IIIA patient (resected, mets &lt;1 mm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine imaging</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>Adjuvant Rx</td>
<td>No</td>
<td>No</td>
<td>?</td>
</tr>
</tbody>
</table>
“While there is interest in newer prognostic molecular techniques such as gene expression profiling…routine (baseline) prognostic genetic testing of primary cutaneous melanomas…is not recommended outside of a clinical study (trial).”

“…difficulty in embracing gene expression profiling…illustrated by the inconsistency of results across studies aimed at defining the most predictive gene sets for melanoma.”

Referring specifically to the 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”
Clinical utility of the GEP test

- GEP test may identify subset of stage I/II patients with higher risk of distant metastasis (than indicated by conventional staging parameters).
- Improved prognostic information may be useful for patients.
- However:
  - Not clear which lesions should be sent for the test.
  - Unclear what actions (if any) should be taken based on GEP test results.
  - No FDA-approved therapies for a SLNB- Class 2 GEP patient.
- GEP test is not a surrogate for SLNB.
- Need for prospective trials with long-term clinical follow-up in order to allow its wide acceptance and integration into staging schemes.

Melanoma deaths
SLNB +
Class 2

LN involvement
Predicts regional failure
Predicts distant mets
Hematogenous spread

? Overlap for thin MM
Questions?