THE ROLE OF GENETIC TESTING IN MELANOMA AND OTHER MELANOCYTIC NEOPLASMS

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Disclosures

I do not have any relevant conflicts of interest.
Genetic Testing

- Germline tests on patient to see whether there is a mutation that may potentially be heritable or carry risks
Genetic Testing

• (Somatic mutation on tumor itself to help aid in diagnosis or prognosis of that specific lesion are not being covered in this talk)
About 10% of patients with melanoma have a positive family history
• Are all of these from a heritable mutation?
• Is the heritable mutation one that has been identified?
Germline tests

About 10% of patients with melanoma have a positive family history

• Is the identifiable mutation one with a currently available commercial test?
• Is it helpful to know if the pt has an identifiable mutation?
• Is it potentially negative to learn that a patient has an identifiable mutation?
Germline tests

Is it helpful to know if the patient has an identifiable mutation?
Not necessarily:

• Pt does not have living blood relatives
• Family members will refuse testing
• Even blood relatives without an identified familial mutation are still at increased risk
Is it potentially negative to learn that a patient has an identifiable mutation?

- “non-informative” vs negative
- Will patient find a non-informative result to be falsely reassuring?
- Studies have not found this to be true
Germline tests

Best practice to identify a specific, relevant mutation

- **Targeted testing**
  - Don’t order a random barrage of tests

- **Our system at Penn:**
  - Patients have to meet with a geneticist or genetic counselor and have pre-test counseling
  - Patients are encouraged to have a post-test meeting with a genetic counselor to review the test results in person
Germline tests

Best to start with the person who is most likely to have a positive result
  • That may not be your patient
Who is more likely to have a heritable mutation?

- More affected family members
  - More 1\textsuperscript{st}-degree family members
  - Multiple generations
- Multiple primary melanomas
  - Especially in multiple family members
- Earlier onset
  - Before age 40 or age 45
- Associated cancers or other aspects of syndrome
Germline tests

- CDKN2A
- BRCA2
- BAP1
CDKN2A

• CDKN2A (cyclin-dependent kinase 2A)
  • Encodes p16, p14(ARF)
  • Rare in general population
  • 3 – 10% of multiple primary melanoma patients
  • 20 – 40% of patients with 3+ family members with melanoma
  • “High-penet trance” gene
    • But penetrance varies by geographic location
CDKN2A

- CDKN2A (cyclin-dependent kinase 2A)
  - Associated cancers
    - Pancreatic cancer
    - Upper airway cancer
  - Astrocytoma
    - Melanoma-Astrocytoma Syndrome
CDKN2A

• Who should get tested for CDKN2A mutation?
  • AAD:
    • 3 or more blood relatives on same side of family
      • Either invasive melanoma or pancreatic cancer
    • 3 or more melanomas in same person, with at least one before age 45
  • Our system:
    • Likelihood score
CDKN2A

<table>
<thead>
<tr>
<th>Features</th>
<th>Points</th>
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<tbody>
<tr>
<td>No of family members with melanoma*</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
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<tr>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>≥4</td>
<td>12</td>
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<tr>
<td>No of family members with MPMs*</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
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<tr>
<td>≥2</td>
<td>10</td>
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<td>Median age at primary diagnosis</td>
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<tr>
<td>≥50 years</td>
<td>0</td>
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<td>&lt;50 years</td>
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<tr>
<td>Presence of pancreatic cancer</td>
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<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>9</td>
</tr>
<tr>
<td>Presence of upper airway cancer</td>
<td></td>
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<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
</tr>
</tbody>
</table>

*First-degree and second-degree relatives of each other, including the index patient. First-degree and second-degree relatives of the index patient and first-degree relatives of patients with melanoma. MPMs, multiple primary melanomas.

Score of 16 or more = 10% likelihood of positive result

Germline tests

- CDKN2A
- BRCA2
- BAP1
• Strongly associated with breast and ovarian cancer
  • 70% will develop breast cancer by age 80
  • 17% will develop ovarian cancer by age 80

• Association with melanoma
  • Studies have found an association
    • but some studies have not found an association

• Also assoc with pancreatic cancer
• Who should get tested for BRCA2 mutation?
  • Usually already addressed by breast/ovarian oncologists
  • BRCA2 identified in 1995, some cancers may pre-date
Who should get tested for BRCA2 mutation?

• **AAD:**
  - No specific recommendation

• **Our system:**
  - Patient has both melanoma AND either breast or ovarian cancer
  - Patient has melanoma and the following in blood relatives:
    - Both breast and ovarian cancer
    - 1 male with breast cancer
    - Add’l factors: Early onset (<40yo, <50yo) or Ashkenazi Jewish heritage
Germline tests

- CDKN2A
- BRCA2
- BAP1
BAP1

• BAP1 (BRCA1 associated protein 1)
  • Chromosome 3p21
  • Tumor suppressor
  • Hallmark is “MBAIT”/ “BAPoma”/ “BIN”
    • Melanocytic BAP1-mutated atypical intradermal tumor
    • BAP1 – inactivated nevus
BAP1

• BAPoma
  • Clinical appearance very similar to dermal nevus
  • Not pigmented
  • Usually first appear in 1st two decades of life
BAP1

• BAPoma
  • Microscopic appearance has some Spitzoid features
    • But NOT synonymous with atypical Spitz tumor!
    • Epithelioid melanocytes
    • Often “ordinary” nevus cells are present
    • Can be lymphoid infiltrate similar to halo reaction
BAP1

• BAPoma
  • Immunostain will show loss of BAP1 expression
  • Most have BRAF mutation
    • Spitz usually has wildtype BRAF
BAP1

• **BAP1 (BRCA1 associated protein 1)**
  • Associated cancers:
    • Mesothelioma
    • Uveal melanoma
    • Cutaneous melanoma
    • Clear cell renal cell carcinoma
    • Meningioma
BAP1

• Who should get tested for BAP1 mutation?
  • AAD:
    • At least 1 MBAIT
      AND
      +FHx for mesothelioma, uveal melanoma, or meningioma
    • 2 or more MBAITs
  • Our system:
    • Similar
Conclusions

• Patients can be tested for CDKN2A, BAP1, and BRCA2.

• These tests should only be ordered if there is a reasonable likelihood of having a mutation. Indiscriminate testing is discouraged.

• Patient selection is key!
Acknowledgements

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Thank you!