Molecular Testing Guidelines for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

Neal I. Lindeman, MD, FCAP, and Marc Ladanyi, MD, FCAP

January 25, 2012
Neal I. Lindeman, MD, FCAP

- Assistant Professor of Pathology at Harvard Medical School
- Clinical specialties in Molecular Diagnostics, Clinical Chemistry, and Anatomic Pathology
- Interests in genetic alterations in solid tumors, particularly involving growth factor signaling pathways in adenocarcinomas of the lung
Marc Ladanyi, MD, FCAP

- Attending Pathologist, Molecular Diagnostics Service, Department of Pathology at Memorial Sloan-Kettering Cancer Center
- William J. Ruane Chair in Molecular Oncology at Memorial Sloan-Kettering Cancer Center and Member in the Human Oncology and Pathogenesis Program
- General clinical expertise in Molecular Genetic Pathology of Cancer with a focus on testing for targeted therapies and sarcoma molecular diagnostics
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Disclosure

- Neal I. Lindeman: no disclosures
- Marc Ladanyi: no disclosures
What? Why? Who?

- International guidelines for molecular testing of lung cancers
- To align practice, expectations, performance

<table>
<thead>
<tr>
<th>Role</th>
<th>CAP</th>
<th>AMP</th>
<th>IASLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steering Cmtee</td>
<td>Jan Nowak</td>
<td>Neal Lindeman</td>
<td>Paul Bunn</td>
</tr>
<tr>
<td>Co-Chair</td>
<td>Phil Cagle</td>
<td>Neal Lindeman</td>
<td>Marc Ladanyi</td>
</tr>
<tr>
<td>Expert Panelist</td>
<td>Sanja Dacic</td>
<td>Dhan Chitale</td>
<td>Dave Kwiatkowski</td>
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<tr>
<td>Expert Panelist</td>
<td>Robert Jenkins</td>
<td>Sebastian Saldivar</td>
<td>Beppe Giaccone</td>
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<tr>
<td>Expert Panelist</td>
<td>Mary-Beth Beasley</td>
<td>Jeremy Squire</td>
<td>Erik Thunnissen</td>
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- CAP Center Admin: John Olsen, Sandi Larsen, Tony Smith, Avtar Lal, Megan Wick
Who?

- CAP Conflict of Interest Policy

- Expert panel exclusions:
  - Giving a sponsored talk
  - Inclusion on a patent claim

- Big Advisory Panel
How?

When?

Panel formation
COI review

Formulation of “key questions”

Literature Search
Nov ‘10

Primary Abstract Review
Dec ‘10

Secondary Literature Review
Dec ‘10

Literature Refresh
Mar ‘11

Tertiary Literature Review
Mar ‘11

Evidence Grading
Aug ‘11

First Draft → Expert Panel
Jun ‘11

Second Draft → Advisors
Aug ‘11

Third Draft → Public comment
Oct‘11

Symposium
Dec ‘10

Outline Preparation/Assignments
Dec ‘10

Public Comment period: Nov 21 - Dec 20, 2011
Rest of timeline

- Expert Panel teleconferences
to discuss Public Comments
  Jan 9 & 18

- Co-chairs make changes and create v4.0
  (April)

- Co-chairs perform review for new studies Jan/Feb
  (Complete by Feb 6)

- Synthesize new studies into existing data analysis
  (Complete by Feb 20)

- Staff update online supplement
  (Complete by March 20)

- Section authors provide citations

- Co-chairs incorporate changes from public comment and share w/ Expert Panel
  (Complete by late March)

- CAP will send for legal review

- Co-chairs make changes and create v4.0
  (April)

- CAP Approval Process
  (May)

- IASLC Approval Process
  (May)

- AMP Approval Process
  (May)

- Submit for Publication (June 1)
to J Mol Diagn, J Thoracic Oncol, Archives of Path
Primary Literature Review

• Medical Library search:
  o Include “lung cancer” AND (EGFR OR ALK OR KRAS OR BRAF) AND (mutation OR (amplification OR polysomy OR “gene copy number”)) OR (rearrangement OR fusion OR translocation OR inversion) OR (IHC OR FISH OR ISH)
  o exclude "expression profiling", "mouse" or "murine", "in vitro" or "cell culture", and "IC50"

• ~1300 abstracts reviewed by co-chairs
  o pertains to who/when to test?
  o pertains to how to test?
  o presents new data (i.e., not review)?

• Reduced to 379 abstracts
## Secondary Review: Writing Panel

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Include</th>
<th>Exclude</th>
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</thead>
<tbody>
<tr>
<td>Clinical Fields</td>
<td>Non-squamous, non-small lung cancer; adenocarcinoma</td>
<td>Squamous carcinoma; small cell</td>
</tr>
<tr>
<td>Applications</td>
<td>EGFR; ALK; EML4; KRAS</td>
<td>BRAF plus all other biomarkers</td>
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<tr>
<td>Applications</td>
<td>Molecular / FISH/ Cytogenetics/ IHC / CISH (or implied) diagnostic techniques</td>
<td>Research techniques; animal models; cell culture</td>
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<tr>
<td>Publications</td>
<td>Randomized controlled trials; co-hort studies; case-controlled studies; case series; observational studies; technical briefs</td>
<td>Case reports; editorials, no primary review or clinical expert review</td>
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<tr>
<td>Relevance</td>
<td>Contributions to cytogenetics or molecular testing for NSCLC</td>
<td>Not relevant to cytogenetics or molecular testing for NSCLC</td>
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<th>Meets Publication or Relevance Criteria</th>
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<td>1 = Yes</td>
<td>1 = Yes</td>
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<tr>
<td>2 = No</td>
<td>2 = No</td>
<td>2 = No</td>
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<tr>
<td>3 = Uncertain (Refer to 3rd reviewer)</td>
<td>3 = Uncertain (Refer to 3rd reviewer)</td>
<td>3 = Uncertain (Refer to 3rd reviewer)</td>
</tr>
</tbody>
</table>
Secondary Literature Review

- 379 articles divided into 12 groups
- Each group reviewed by two panelists
- Full article review
  - Same “key questions”
    - Does it address clinical questions
    - Does it address technical questions
    - What type of publication is it
  - Added question: is it useful?
- Left with about 160 articles
Tertiary Literature Review

- With draft of manuscript in hand
- Point by point assessment of each article and each recommendation
  - Supports
  - Refutes
  - Not relevant/not useful
- Conflicts resolved one-at-a-time
- Literature Refreshers: additional primary literature searches done in March 2011 and Jan 2012
Evidence Grading

• Articles that survive the tertiary review
• Methodologist: Avtar Lal
• Formal evidence grading
• Assess “strength score” of evidence for each recommendation
Enough about the process:
What are the draft recommendations?

CAP-IASLC-AMP
Molecular Testing Draft Guidelines for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors
### Clinical criteria: inadequate predictors

<table>
<thead>
<tr>
<th>AGE</th>
<th>GENDER</th>
<th>TOBACCO</th>
<th>ETHNICITY</th>
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</tr>
<tr>
<td>&gt;65</td>
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<td>West Eurp.</td>
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#### Mutant/No Mutant

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mutant</th>
<th>No Mutant/ Wild type</th>
<th>Risk Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Bae NC 2007</td>
<td>13</td>
<td>20</td>
<td>0.01 (0.01, 0.1)</td>
</tr>
<tr>
<td>Dacic S 2010</td>
<td>22</td>
<td>37</td>
<td>0.05 (0.02, 0.1)</td>
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<td>El-Zammar OA 2009</td>
<td>19</td>
<td>52</td>
<td>0.001 (0.0001, 0.01)</td>
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<tr>
<td>Hsieh MH 2006</td>
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<td>30</td>
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<tr>
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<td>40</td>
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<td>8</td>
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Total events: 224

Test for overall effect: 4.46 (P < 0.0001)

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</tr>
<tr>
<td>Sunaga N 2007</td>
<td>2</td>
<td>21</td>
<td>0.001 (0.0001, 0.01)</td>
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</tbody>
</table>

Total events: 345

Test for overall effect: 4.46 (P < 0.0001)
WHOM to test?
Histology matters

Test any primary lung cancer with adenocarcinoma histology

- May be mixed (adenosq, adeno/small cell)
- NO pure squamous, small cell, neuroendocrine
  - Except maybe incomplete small biopsies
- Poorly differentiated tumors should be tested
- Subtypes of adenocarcinoma not useful
  - Except maybe mucinous

“NSCLC” is an inadequate diagnosis
• Histologic types of lung cancer have distinct sets of driver mutations.

• Unexpected morphologic-molecular associations are usually explained by challenges in pathologic characterization and special clinical settings.

• Recognition of these highly significant associations has implications for utilization and prioritization of molecular testing and elicits new scientific questions.

• What about squamous CA, large cell CA, and small cell CA?
**Molecular and histological classifications of lung cancer inform each other**

- **Squamous carcinoma**: EGFR/KRAS mutations do not occur in pure pulmonary squamous carcinoma.

- **Large cell carcinoma**: not a single entity - lineage-specific immunomarkers define subsets with a distinct spectrum of driver oncogene mutations.

- **Small cell carcinoma**: EGFR/KRAS mutations occur only in rare cases with a clonal relationship to adenocarcinoma.
Limitations of morphology in the diagnosis of ADC vs SQCC: Poorly differentiated areas of ADC and SQCC are morphologically indistinguishable.

**ADC**

**SQCC**

| TTF-1+ | p63+ |
**TTF-1 and p63**

- Multiple recent studies show that IHC is extremely helpful in distinguishing ADC vs SQCC
- TTF-1 and p63 are developmental transcription factors that function as lineage-determining “master regulators”
- Optimal 2-Marker Panel for distinguishing ADC and SQCC: TTF-1 + ΔNp63

Clarifying the spectrum of driver oncogene mutations in biomarker-verified squamous carcinoma of lung

- *EGFR/KRAS* mutations do not occur in pure SQCC
- Mutations occur in both components of AD-SQC, which in small specimens cannot be distinguished from pure SQCC
- Solid ADC can mimic SQCC morphologically, but this is readily clarified by IHC
- Samples diagnosed as “SQCC” harboring these mutations are due to pitfalls in pathologic diagnosis of AD-SQC and ADC, which can largely be resolved by comprehensive pathologic assessment incorporating IHC markers

Large cell CA: WHO 2004 Definition

Undifferentiated NSCLC that lacks morphologic features of adenocarcinoma or squamous cell carcinoma.
IHC-based reclassification of 90 LCC

<table>
<thead>
<tr>
<th></th>
<th>TTF-1+</th>
<th>TTF-1-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
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<td>p63(ΔN)-</td>
<td>49 (54)</td>
<td>20 (22)</td>
<td>69 (76)</td>
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<tr>
<td>p63(ΔN)+</td>
<td>2 (2)*</td>
<td>19 (21)</td>
<td>21 (23)</td>
</tr>
<tr>
<td>Total</td>
<td>51 (56)</td>
<td>39 (43)</td>
<td></td>
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</table>

* TTF-1 and p63 (dN) reactivity in distinct cell populations

Rekhtman N et al. **Distinct spectrum of driver oncogene mutations in histogenetic subsets of large cell carcinoma of the lung defined by lineage-specific immunomarkers.** (to be submitted)

**Pie Chart**

- **IHC-ADC**: 54%
- **IHC-SQCC**: 21%
- **IHC-AD-SQC**: 2%
- **IHC-NULL**: 22%
Example of LCC reclassified by IHC as ADC
Example of LCC reclassified by IHC as SQCC
### Distribution of mutations according to IHC-defined lineage in LCC

<table>
<thead>
<tr>
<th>Mutation*</th>
<th>IHC-defined subset of LCC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADC† (n=51)</td>
</tr>
<tr>
<td><strong>EGFR</strong></td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>KRAS‡</strong></td>
<td>20 (39%)</td>
</tr>
<tr>
<td><strong>BRAF</strong></td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

†includes 2 adenosquamous carcinomas

---

Rekhtman N et al. *Distinct spectrum of driver oncogene mutations in histogenetic subsets of large cell carcinoma of the lung defined by lineage-specific immunomarkers.* (to be submitted)
Large Cell CA: conclusions

- The majority of LCC are readily reclassified as poorly-differentiated ADC or SQCC by a simple but robust panel of IHC markers, revealing subsets with a distinct distribution of therapeutically-relevant driver mutations.

- IHC-based reclassification of LCC can therefore guide testing for targeted therapy selection.

Rekhtman N et al. *Distinct spectrum of driver oncogene mutations in histogenetic subsets of large cell carcinoma of the lung defined by lineage-specific immunomarkers.* (to be submitted)
EGFR mutations do not occur in conventional (pure de novo) SCLC (MSKCC data: 0/71).

EGFR mutations do occur in rare SCLC with a clonal relationship to ADC in the 2 settings:
- 1) de novo combined SCLC/ADC or
- 2) ADC→SCLC transformation as an EGFR TKI acquired resistance mechanism (rare)
Which sample to test?

- Quality and quantity are key determinants
  - A cellular FNA is better than a necrotic resection

- Primary vs. metastasis
  - Quality is determinant, tempered by interval therapy
    - If metastasis after initial TKI response, then test metastasis

- Multiple primaries
  - If histologies differ, then test BOTH/ALL
    - Patients will benefit even if 1 of multiple tumors responds

- Testing multiple areas in a tumor is unnecessary
WHEN to test?

- Advanced stage: at diagnosis, ASAP
  - Unless patient is hospice/palliative care only

- Early stage: discuss with your oncologists
  - If testing not done now, save material!
WHEN should results be available?

- TKI therapy no longer empirically started without evidence of a sensitizing mutation

- TAT for delivery of blocks/unstained slides:
  - In-house: 24 hours
  - Outside: 3 working days

- TAT once sample is received within the lab:
  - Goal: 10 working days
  - Slower labs: make a faster method available when needed
How should samples be processed?

**Fixation**

- Formalin-fixed DNA is typically adequate if <300 bp
- Heavy metal fixatives and acidic fixatives or decalcifying solutions are not acceptable
- Fixation times established in validation
- Cell blocks recommended for cytology samples
- Each fixative should be validated by the lab
- Indicate suboptimal fixation in the report
Minimum Tumor content

• Each lab must determine during validation
  o GENERAL goals: 500 cells, 50% tumor

• Pathologist must review each section

• Enrichment
  o Gross dissection is recommended
  o Laser capture can introduce errors

• Small samples
  o Testing in duplicate is recommended
  o WGA can introduce errors

• Low positive control in each run
### How to test for EGFR?

**Molecular Diagnosis!**

<table>
<thead>
<tr>
<th><strong>Mol Dx</strong></th>
<th><strong>FISH</strong></th>
<th><strong>IHC</strong></th>
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<tr>
<td><strong>Risk Ratio</strong></td>
<td><strong>Risk Ratio</strong></td>
<td><strong>Risk Ratio</strong></td>
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<tr>
<td><strong>M-H, Random, 95% CI</strong></td>
<td><strong>M-H, Random, 95% CI</strong></td>
<td><strong>M-H, Random, 95% CI</strong></td>
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<td>3.61 [1.91, 6.83]</td>
<td>4.69 [1.80, 12.29]</td>
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<td>6.80 [2.72, 17.00]</td>
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<td>7.10 [2.06, 25.90]</td>
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<td>1.50 [0.48, 3.24]</td>
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<td>4.67 [0.92, 23.07]</td>
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<td>9.00 [1.47, 54.89]</td>
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<td>22.86 [5.20, 98.99]</td>
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<td>1.68 [1.06, 2.68]</td>
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<td>3.60 [1.72, 7.41]</td>
<td>3.72 [1.67, 8.79]</td>
<td>4.64 [2.68, 8.09]</td>
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### 5.9.1 Response Rate

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
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<td>54</td>
<td>7</td>
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<tr>
<td>C</td>
<td>13</td>
<td>23</td>
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<tr>
<td>D</td>
<td>11</td>
<td>122</td>
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<td>38</td>
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<tr>
<td>Endo H 2006</td>
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<td>11.3%</td>
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<tr>
<td>Miller VA 2008</td>
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<td>39</td>
<td>11.5%</td>
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<td>1</td>
<td>14</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td>265</td>
<td>100.0%</td>
<td>1.48 [0.90, 2.44]</td>
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</table>

Total events: 110

**Heterogeneity:** Tau² = 0.30; Chi² = 18.55, df = 9 (P = 0.03); I² = 51%

**Test for overall effect:** Z = 1.55 (P = 0.12)

### 5.9.3 Disease Control

<table>
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<tr>
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<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahn MJ 2008</td>
<td>30</td>
<td>54</td>
<td>10</td>
<td>21</td>
<td>19.4%</td>
</tr>
<tr>
<td>Argrins A 2006</td>
<td>6</td>
<td>20</td>
<td>4</td>
<td>15</td>
<td>4.3%</td>
</tr>
<tr>
<td>Endo H 2006</td>
<td>20</td>
<td>26</td>
<td>13</td>
<td>26</td>
<td>26.1%</td>
</tr>
<tr>
<td>Hirsch FR 2007</td>
<td>62</td>
<td>120</td>
<td>22</td>
<td>80</td>
<td>32.0%</td>
</tr>
<tr>
<td>Lara-Guerra H 2009</td>
<td>18</td>
<td>29</td>
<td>1</td>
<td>6</td>
<td>1.5%</td>
</tr>
<tr>
<td>Sholl LM 2010</td>
<td>10</td>
<td>13</td>
<td>9</td>
<td>18</td>
<td>16.6%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>262</td>
<td>166</td>
<td>100.0%</td>
<td>1.55 [1.24, 1.94]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 146

**Heterogeneity:** Tau² = 0.00; Chi² = 3.48, df = 5 (P = 0.63); I² = 0%

**Test for overall effect:** Z = 3.86 (P = 0.0001)

### 5.9.4 Survival at Year 1

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirsch FR 2007</td>
<td>67</td>
<td>120</td>
<td>30</td>
<td>80</td>
<td>100.0%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>120</td>
<td>80</td>
<td>100.0%</td>
<td>1.49 [1.08, 2.06]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 67

**Heterogeneity:** Not applicable

**Test for overall effect:** Z = 2.40 (P = 0.02)

Test for subgroup differences: Chi² = 0.06, df = 2 (P = 0.97), I² = 0%

---

**Notes:**

- The table and diagram likely represent a meta-analysis showing the effectiveness of different treatments or conditions in terms of response rates and disease control.
- The data include risk ratios and confidence intervals, along with tests for heterogeneity and overall effects.
- The figure may be a forest plot or other visual representation of the data, illustrating the comparison between different treatment groups or conditions.
How to test for EGFR?

• KRAS wt status **by itself** is not useful for EGFR therapy

• **No specific platform is recommended**

  • Predicate or historical reference method:
    o Sanger sequencing
    o Acceptable methods must be AS SENSITIVE or better

• More sensitive (1-10%) testing must be available
  o Either in-house or send-out when needed
How is sensitivity defined?

- **Functional Sensitivity** = lowest mutant tumor content that is detected with **100% precision** during validation.

- **Lower limit of detection** = lowest mutant tumor content that can be detected at least once during validation.

- Wild type results from samples with tumor content between functional sensitivity and lower limit of detection should be reported as **inconclusive** – or tested by a more sensitive method.
How is specificity established?

• Ultra sensitive methods may give false positive results
  o Specificity must be carefully established in validation

• Mutations in minor subpopulation: uncertain significance
  o Ideal: test with and without ultra sensitive method
  o Report both mutant, both wt, ultra-sensitive mutant only
    - Correlate results with tumor content in the report

• Sequencing should be performed in both directions
Logistics affect method selection

- Discuss with your clinicians!
  - Turnaround time needs
  - Mix of resections, small biopsy, cytology
  - Diversity of sample handling and fixation
  - First-line or second-line therapy
  - Monitoring for resistance
Which mutations to test?

- Exon 19 and Exon 21 alone is inadequate
- All mutations with >1% frequency
  - Exon 18: E709, G719 mutations
  - Exon 19: all deletions and rare insertions
  - Exon 20: insertions, T790M, S768
  - Exon 21: L858R, L861Q, T854
- Rare or never seen before mutations: great caution!
  - Confirm with repeat from a new DNA isolation
- T790M
  - Ultrasensitive method required for resistance testing (5%)
  - Germline testing if T790M detected before treatment
How should ALK be tested?

• ALK FISH test is recommended
  o Role for IHC is still evolving
    − Unmodified IHC with standard ALK antibodies used for anaplastic large cell lymphoma not recommended
    − Enhanced IHC techniques and/or better antibodies could make IHC a viable screening step
  o RT-PCR not recommended as only test
    − Molecular and chromosomal variants
  o Mutation testing in resistance: not yet
ALK FISH

• Split-apart design is recommended
ALK FISH

• Which samples?
  o Tumor percentage less critical
  o At least 50 tumor nuclei
  o Non-overlapping cells

• Who to interpret?
  o Pathologist trained in FISH
  o Technologist trained in pathology
  o Two independent reviewers?
ALK FISH Interpretation

- Two kinds of positive signals
  - "Split": >=2 probe diameter between signals
    - Narrow splits are common in non-rearranged samples!
  - Excess 3’ signal (loss of 5’ signal)

- Positive sample: >15% of cells
  - Borderline samples: 10-15% cells, consider repeat testing

- Polysomy without rearrangement
  - Common, not considered significant
Testing for other genes is considered of lower priority

- Clinical trials, but not standard care
  - KRAS, BRAF, ERBB2, PIK3CA, MET
- Markers of chemotherapy response
  - ERCC1, TS, RRM1
Testing algorithms

• Critical to understand TAT needs
  o Testing should be completed within 10 days
  o No single algorithm is recommended

• EGFR $\rightarrow$ ALK if neg

• EGFR screen first (i.e., melt curve)
  o Reflex to ALK or EGFR confirmation

• KRAS $\rightarrow$ EGFR if neg $\rightarrow$ ALK if neg
Reporting

• Standard identifiers and demographics

• Pathology review
  o Tumor content
  o Was it dissected?

• Results
  o Standard nomenclature and colloquial name
  o If weak positive signal, indicate as such
  o Incidental findings: SNPs
  o Explain inconclusive or insufficient results
  o List each result (mutant or wild type)
Reporting (cont’d)

• Interpretation
  o Clinical significance of result and recommendation
  o Clearly explain incidental findings
  o Correlate with tumor content when appropriate

• Technical details
  o Enable another lab to understand and explain discrepancies
  o List of mutations/exons tested
  o Sensitivity

• ALK reports
  o Assay design
  o Number and percent of cells with each finding
  o Report formally and colloquially
  o Incidental findings
  o Interpretation
  o Recommendations
Validation

- Similar to other molecular assays
- Validate all steps, including dissection
- Validate all sample types, not all tissues
- Sensitivity is critical
  - More than one sample should be used
  - Replicates of dilutions should be performed
- Specificity is critical for ultra-sensitive methods
- International practices differ
Next in the Series of Free PHC Webinars

- **Molecular Diagnosis of Lung Cancer,**
  Tuesday, February 21, 12:00-1:00 pm CT
  - John Iafrate, MD, PhD, FCAP

- **Go to** [www.cap.org/institute](http://www.cap.org/institute) **For All Upcoming Webinars!**

- **Past Webinars Available Now Online at** [www.cap.org/institute](http://www.cap.org/institute)
  - Clinical Use of Whole Genome and Whole Exome Sequencing Today
  - Who Wants to Eat Your PHC Lunch?
  - Validating Whole Slide Imaging Systems for Diagnostic Use in Pathology
  - The Why, What and How of Identifying Patients at Risk
  - How to Have Successful Patient Interactions
  - Next-Generation Sequencing for the Clinical Laboratory
  - Accountable Care Organizations
## CAP Learning – Other Molecular Oncology CME Activities

<table>
<thead>
<tr>
<th>Course</th>
<th>Learning Objectives</th>
</tr>
</thead>
</table>
| **Molecular Pathology: An Introduction to DNA Technology and Diagnostic Applications (SAM eligible)**<br>CME/SAM – 2.0 | - Identify potential application of molecular pathology  
- Describe the chemical structure and properties of DNA and RNA  
- Explain the different types of genetic variations  
- Identify diagnostic techniques in molecular pathology |
| **Archives Applied: KRAS (SAM eligible)**<br>CME/SAM – 1.0             | - Identify whether anti-EGFR therapy is an appropriate treatment method for a patient case  
- Describe advantages and limitations of specific KRAS mutation testing methods  
- Identify the appropriate elements to include in the report for a patient case  
- Describe the current role of KRAS mutation testing for management of patients with metastatic colorectal cancer |
| **Archives Applied: Molecular Test Validation (SAM eligible)**<br>CME/SAM = 1.0 | - Identify the appropriate:  
  - Test parameters for an analytic quantitative or qualitative test  
  - Clinical performance characteristics for test validation  
  - Performance characteristics for a quantitative or qualitative test  
  - Elements to include in test validation documentation  
  - Identify pre-validation considerations for a proposed molecular pathology test |
| **Archives Applied: Molecular Diagnostics of Soft Tissue Tumors (SAM eligible)**<br>CME/SAM = 1.0 | - Recognize which genetic alterations seen in soft tissue tumors are amenable to molecular diagnostics using routine clinical genetic approaches  
- Describe characteristics of chromosomal translocations in soft tissue sarcomas  
Identify the advantages and limitations of conventional cytogenetic analysis for soft tissue tumors  
- Identify approaches for assessing inactivation of a tumor suppressor gene, for example the SMARCB (INI1) in soft tissue tumors  
- Identify the advantages and limitations of molecular cytogenetic analysis for soft tissue tumors |
## CAP Learning – Other Molecular Oncology CME Activities

<table>
<thead>
<tr>
<th>Course</th>
<th>Learning Objectives</th>
</tr>
</thead>
</table>
| **Molecular Testing for AML Cases**       | - Recognize molecular oncology knowledge and skills required of pathologists that can mitigate problems and enhance patient care with respect to specimen handling  
- Realize the effects that appropriate specimen handling and communication throughout all stages of diagnosis have in enhancing patient care  
- Reflect on your own knowledge and skills in specimen handling and patient care, and identify what can help you and your practice be more effective in these areas of molecular oncology                                                                 |
| CME – .5                                  |                                                                                                                                                                                                                       |
| **BRAF Mutation Testing in Melanoma**     | - Follow quality assurance policies and procedures to ensure adequate sample collection and proper handling techniques for molecular oncology tests  
- Use appropriate result reporting principles for incorporating molecular test results into surgical pathology reports                                                                                           |
| CME – .5                                  |                                                                                                                                                                                                                       |
| **Molecular Testing for Lymphoma Cases**   | - Recognize molecular oncology knowledge and skills required of pathologists that can mitigate problems and enhance patient care with respect to specimen handling  
- Realize the effects that appropriate specimen handling and communication throughout all stages of diagnosis have in enhancing patient care  
- Reflect on your own knowledge and skills in specimen handling and patient care, and identify what can help you and your practice be more effective in these areas of molecular oncology                                                                 |
| CME – .5                                  |                                                                                                                                                                                                                       |
| **Adenocarcinoma and EGFR and KRAS Mutation Testing** | - Recognize the indications for EGFR and KRAS molecular testing as they pertain to non-small cell lung cancer  
- Interpret molecular diagnostic test results and correlate them with the diagnosis pertaining to non-small cell lung cancer                                                                                       |
# CAP Learning – Other Molecular Oncology CME Activities

<table>
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<tr>
<th>Course</th>
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</tr>
</thead>
</table>
| Molecular Diagnosis of Ewing Sarcoma       | - Review sample requirements and handling for RT-PCR, FISH, and cytogenetic analysis as they pertain to evaluating mesenchymal neoplasms  
- Describe the advantages and limitations of genetic approaches commonly used in the classification of mesenchymal neoplasms to include conventional karyotyping, FISH, and RT-PCR |
| CME - .5                                    |                                                                                                                                                                                                                      |
| BPFT Testing Self Study                    | - Explain the ASCO-CAP ER/PR Testing Guidelines and their implications for lab procedures, test results and patient care.                                                                                          
- Explain the ASCO-CAP HER2 Testing Guidelines and their implications for lab procedures, test results and patient care.  
- Determine if the assay and tissue sample are appropriately matched per the ASCO/CAP Guidelines.  
- Explain the biology of fixation interactions with assay performance.  
- Explain the potential use of molecular analysis in patient care decisions.  
- Mitigate problems and enhance patient care with respect to specimen handling |
| CME /SAM – 2.5                              |                                                                                                                                                                                                                      |
| HER2 FISH Test Interpretation Accuracy     | - Accurately interpret HER2 FISH tests.                                                                                                                                                                               
- Correct for HER2 FISH interpretative errors.  
- Recognize the relationship between HER2 FISH test results and patient treatment.                                                                       |
| CME/SAM – 1.5                               |                                                                                                                                                                                                                      |
| BPFT Reporting                              | - Apply the ASCO-CAP ER/PR and HER2 Guideline criteria to all reports in a standardized manner.                                                                                                                     
- Create consistent, standardized and integrated reports.                                                                                                      
- Remediate inconsistent data and provide a resolution in an integrated report.                                                                               
- Create patient friendly reports.                                                                                                                             
- Use formatting techniques to create clear and understandable reports.                                                                                      |
<p>| CME/SAM – 1.5                               |                                                                                                                                                                                                                      |</p>
<table>
<thead>
<tr>
<th>Course</th>
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</tr>
</thead>
</table>
| **ER IHC Test Interpretation Accuracy**     | -Plan and perform a proper ER IHC test validation.  
- Accurately perform and interpret ER IHC tests, including the proper evaluation of appropriate controls and test tissues.  
- Evaluate and integrate ER staining patterns with clinical and morphologic findings.  
- Identify the relationship and impact of ER IHC test results on patient treatment. |
| **HER2 IHC Test Interpretation Accuracy**   | -Plan and perform a proper HER2 IHC test validation in accordance with ASCO-CAP guidelines for HER2 testing.  
- Accurately perform and interpret HER2 IHC tests, including the proper evaluation of appropriate controls and test tissues.  
- Evaluate and integrate HER2 staining patterns with clinical and morphologic findings to help improve concordance with HER2 FISH results.  
- Identify the relationship and impact of HER2 IHC test results on patient treatment. |

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Reminder: CAP Learning Portal Launches

CAP Learning Portal

- The CAP Learning Portal landing page on the cap.org website replaces the current Education Programs page design. A user must log into cap.org in order to access further information.

- The CAP Learning Portal includes new tools to support the learning needs of pathologists such as:
  - Learning Options search/catalog
  - Competency Model for Pathologists
  - Personal Progress Check (member only tool)
  - My Learning Plan (member only tool)
  - Help Center

- Benefits
  - Increase effectiveness to plan and manage learning
  - Increase efficiency to target learning needs and identify premium learning solutions
  - Increase satisfaction with learning solutions that meet specific learner needs
  - Increase capability to maintain professional certifications
To learn more...

- For more details and to register for/access Molecular Oncology educational offerings:
  1. Log in to the cap.org website
  2. Click on Launch Portal
  3. Click on the Learning Options tab
  4. Type Molecular Oncology in the Search box

A list of available learning options displays
This lecture on “Molecular Testing Guidelines for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors” presented by Neal I. Lindeman, MD, FCAP and Marc Ladanyi, MD, FCAP and Co-sponsored by AMP.

For comments about this webinar or suggestions for upcoming webinars, please contact Jill Kaufman, PhD, Director of Personalized Health Care at jkaufma@cap.org