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Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment with Targeted Tyrosine Kinase Inhibitors

Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and the Association for Molecular Pathology

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METHODS USED TO PRODUCE THE GUIDELINE

Panel Composition

The College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) convened an expert panel (EP) consisting of practicing pathologists, oncologists, and a methodologist to review and update the *CAP-IASLC-AMP Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors*,[1-3] an evidence-based guideline published in 2013 to help establish standard molecular marker testing, guide targeted therapies, and advance personalized care for lung cancer patients. All three organizations appointed a representative to serve as a co-chair, with one taking a leadership role. All three organizations approved the appointment of panel members. The EP and the methodologist performed the systematic evidence review. An advisory panel (AP) of pathologists, oncologists, and patient advocates also helped in the development of the guideline. The role of the AP members was to provide guidance and feedback on the key questions for the literature search, vet the draft guideline statements prior to the public comment period, and to review and provide feedback for the manuscript and supplemental digital content.

Conflict of Interest (COI) Policy

Prior to acceptance on the expert or advisory panel, potential members completed a joint guideline conflict of interest (COI) disclosure process, whose policy and form (in effect January 2015) required disclosure of material financial interest in, or potential for benefit of significant value from, the guideline's development or its recommendations 12 months prior through the time of publication. The potential members completed the COI disclosure form, listing any relationship that could be interpreted as constituting an actual, potential, or apparent conflict.

The CAP/IASLC/AMP joint guideline conflicts of interest policy uses the following criteria to define relationships that could be interpreted as constituting an actual, potential, or apparent conflict:
1. Stock options or bond holdings in a relevant commercial entity or self-directed pension plan
2. Research grants from a relevant commercial entity
3. Employment (full or part-time) by a relevant commercial entity
4. Ownership or partnership in relevant corporate entities, including equities and stock options
5. Consulting or advisory fees from relevant commercial entities
6. Other remuneration from relevant commercial entities, including free or discounted products or equipment, trips, accommodations, tickets to sports or entertainment events, etc.
7. Non-remunerative positions of influence in a relevant commercial entity such as officer, board member, trustee, spokesperson, advisor
8. Royalties from relevant commercial entities
9. Intellectual property rights, i.e., patents issued or pending
10. Lecture or speaker fees/honoraria from relevant commercial entities
11. Other relationships, e.g., research collaborations, to be identified with details, as needed

All project participants were required to disclose conflicts prior to beginning and continuously throughout the project's timeline. All disclosed conflicts were reviewed by a joint COI Review Committee composed of staff officials from each of the respective organizations. The joint COI Review Committee agreed, by majority vote, on any resolution of actual or perceived conflicts of interest.

Only one of the co-chairs could receive research support from a relevant commercial entity (no other relevant relationship was allowed). At least 51% of the EP had no existing or future relationships planned with relevant commercial entities during the development and publication of the practice guidelines. For the remaining 49%, such relationships did not preclude EP membership. At the discretion of the co-chairs, these individuals were asked to recuse

themselves from discussing topics and abstained from voting on any decisions or approvals relevant to their relationships. EP members' disclosed conflicts are listed in the appendix of the manuscript. Advisory panel members had a disclosure requirement, but conflicts were not subject to management by the COI Review Committee.

CAP, IASLC, and AMP provided funding for the administration of the project; no industry funds were used in the development of the guideline. All panel members volunteered their time and were not compensated for their involvement, except for the contracted methodologist.

Literature Review and Analysis

The current guideline was composed of an assessment of the original 2013 guideline statements based on new evidence, and a systematic review of new key questions focused on additional biomarkers not included in the original guideline.

The EP and patient advocates met in person on two occasions: to define the scope and key questions (March 21, 2015 in Boston, Massachusetts) and to review evidence tables and draft recommendations (February 26-27, 2016 in Bethesda, Maryland). The co-chairs met an additional time (January 9, 2016, Denver, Colorado) to synthesize the drafted manuscript. In addition, the EP met three times through teleconference webinars from May 27, 2015 to September 26, 2016. Additional work was completed via electronic mail.

During the first in-person meeting, the EP was tasked to address the overarching key questions "Are there any new studies that would change or refute the 2013 recommendation statements?" In addition, the panel also formed the additional key questions on which to base the literature search:

Key questions 1-4 relate to patients diagnosed with non-squamous, non-small cell lung cancer of all stages.

1. What other genes, previously not addressed, should be tested in lung adenocarcinoma?
    - I. In patients who are being considered for therapy with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors or MEK inhibitors;
        - i. What demographic, histopathologic and clinical characteristics should be used to select patients for *KRAS* molecular testing?
        - ii. Are there downstream improvements in clinical outcomes when individuals are tested for mutation within the *KRAS* gene, compared to when individuals are not tested for *KRAS* mutation?
        - iii. When screening for mutations within the *KRAS* gene, what are the clinical performance characteristics of the available assays?
    - II. In patients who are being considered for therapy with ROS1 tyrosine kinase inhibitors;
        - i. What demographic, histopathologic and clinical characteristics should be used to select patients for *ROS1* molecular testing?
        - ii. Are there downstream improvements in clinical outcomes when individuals are tested for any rearrangement/translocation within the *ROS1* gene, compared to when individuals are not tested for *ROS1* mutation?
        - iii. When screening for rearrangement/translocation within the *ROS1* gene, what are the clinical performance characteristics of the available assays, including, fluorescence in situ hybridization (FISH), immunohistochemistry (IHC) and advanced sequencing?
    - III. In patients who are being considered for therapy with RET tyrosine kinase inhibitors;
        - i. What demographic, histopathologic and clinical characteristics should be used to select patients for *RET* molecular testing?
        - ii. Are there downstream improvements in clinical outcomes when individuals are tested for fusion and rearrangement/translocation within the *RET* gene, compared to when individuals are not tested for *RET* mutation?

iii. When screening for fusion and rearrangement/translocation within the *RET* gene, what are the clinical performance characteristics of the available assays, including FISH, IHC, reverse transcriptase polymerase chain reaction (RT-PCR), digital polymerase chain reaction (PCR), and advanced sequencing?

IV. In patients who are being considered for therapy with MET tyrosine kinase inhibitors;
   i. What demographic, histopathologic and clinical characteristics should be used to select patients for *MET* molecular testing?
   ii. Are there downstream improvements in clinical outcomes when individuals are tested for expression, overexpression, amplification, or mutations of the *MET* gene, compared to when expression levels are not tested within individuals?
   iii. When screening for expression, overexpression, amplification, or mutations of the *MET* gene, what are the clinical performance characteristics of the available assays, including FISH, IHC and advanced sequencing?

V. In patients who are being considered for therapy with BRAF inhibitors or EGFR tyrosine kinase inhibitors;
   i. What demographic, histopathologic and clinical characteristics should be used to select patients for *BRAF* molecular testing?
   ii. Are there downstream improvements in clinical outcomes when individuals are tested for mutation within the *BRAF* gene, compared to when individuals are not tested for *BRAF* mutation?
   iii. Are there differences in clinical outcomes for patients with different alterations of the *BRAF* gene?
   iv. When screening for mutation within the *BRAF* gene, does IHC provide equivalent performance characteristics to molecular based methods?

VI. In patients who are being considered for therapy with HER2/ERBB2 tyrosine kinase inhibitors;
   i. What demographic, histopathologic and clinical characteristics should be used to select patients for *HER2/ERBB2* molecular testing?
   ii. Are there downstream improvements in clinical outcomes when individuals are tested for mutation and amplification/overexpression of the *HER2/ERBB2* gene, compared to when *HER2/ERBB2* mutations are not tested within individuals?
   iii. When screening for mutations and amplification/overexpression of the *HER2/ERBB2* gene, what are the clinical performance characteristics of the available assays, including FISH, IHC and advanced sequencing?

VII. When conducting molecular testing of *KRAS*, *ROS1*, *RET*, *MET*, *BRAF* and *HER2/ERBB2*, what technical validation experiments should be performed in order for an assay to be considered safe and reliable for use in patient care?

2. Is immunohistochemistry reliable for screening for *ALK* translocations?

VIII. When screening for *ALK* translocations, does IHC provide equivalent clinical performance characteristics when compared to FISH and ribonucleic acid (RNA)/ deoxyribonucleic acid (DNA) sequencing methods for *ALK* translocations?

IX. When considering IHC antibodies for screening of *ALK* translocations, is there a difference in clinical performance characteristics for ALK1, 5A4, or D5F3 antibodies and/or detection platforms?

X. When comparing IHC techniques for screening of *ALK* translocations, do any emerging techniques (anchored PCR, ultrasensitive detection systems) provide superior clinical performance characteristics?

XI. If potential *ALK* translocations are detected in patients by a sensitive IHC assay, are the clinical performance characteristics sufficient, or does the *ALK* translocation need to be confirmed by an orthogonal method?

3. In patients who are undergoing treatment with targeted tyrosine kinase inhibitors, what are the types and rates of secondary (acquired clinical) resistance?
   XII. Does pre-treatment discovery of de novo resistance-related mutations improve clinical outcomes?
   XIII. Does evaluation of rebiopsy specimens improve clinical outcomes?
   XIV. When assessing the resistance-related mutations, what are the clinical performance characteristics of the emerging technologies, including rebiopsy, next generation sequencing (NGS), and circulating DNA or circulating tumor cells (CTC)?

4. What are the clinical performance characteristics of circulating DNA/CTC in plasma when used for diagnosis of primary lung adenocarcinoma or relapse?

5. Are there biomarkers that are predictive of clinical outcome in squamous and small cell carcinomas?

All EP members participated in the systematic evidence review (SER). Each level of the SER (title-abstract review, full text review, and data extraction) was performed in duplicate by two members of the EP or one member of the EP and a methodologist. All EP members and a methodologist performed adjudication of the conflicts. Articles meeting the inclusion criteria were assessed for strength of evidence, methodological rigor, and confirmation of validity by the methodologist. Supplemental Figure 1. Literature Review Flow Diagram 1 and 2 display the results of the literature review. All articles were available as discussion or background references. All EP members participated in developing draft recommendations, reviewing open comment feedback, finalizing and approving final recommendations and writing/editing of the manuscript.

Peer Review

A public open comment period was held from June 28 through August 2, 2016. The public commented on all the statements from the 2013 guideline and 20 new draft statements from the additional key questions. The public comment was posted online on the AMP web site. The open comment period was publicized via joint society communications announcements and the following societies, patient advocacy groups, and stakeholders were deemed to have interest:

Medical Societies:

- College of American Pathologists (CAP)
- International Association for the Study of Lung Cancer (IASLC)
- Association for Molecular Pathology (AMP)
- American Association for Clinical Chemistry (AACC)
- American College of Chest Physicians (CHEST)
- American College of Medical Genetics and Genomics (ACMG)
- American Society for Clinical Oncology (ASCO)
- American Society for Clinical Pathology (ASCP)
- American Society for Investigative Pathology (ASIP)
- American Society of Cytopathology (ASC)
- American Thoracic Society (ATS)
- Arthur Purdy Stout Society (APSS)
- Association of Community Cancer Centers (ACCC)
- Association of Directors of Anatomic and Surgical Pathology (ADASP)
- Association of Pathology Chairs (APC)
- British Thoracic Oncology Group
- Canadian Association of Pathologists (CAP-APC)
- European Society for Medical Oncology (ESMO)
- European Society of Thoracic Surgeons

- Indian Society for the Study of Lung Cancer
- International Thoracic Oncology Nurses Forum
- Korean Association for the Study of Lung Cancer
- National Comprehensive Cancer Network (NCCN)
- National Lung Cancer Forum for Nurses
- Papanicolaou Society of Cytopathology (PSC)
- Pulmonary Pathology Society (PPS)
- Quality Initiative in Interpretive Pathology (QIIP) Canadian Partnership Against Cancer
- Russian Society of Clinical Oncology
- Sociedade Brasileira de Cirurgia Torácica (Brazilian Society of Thoracic Surgery)
- Sociedade Brasileira de Patologia (Brazilian Society of Pathology)
- Society to Improve Diagnoses in Medicine (SIDM)
- The Japan Lung Cancer Society
- United States & Canadian Academy of Pathology (USCAP)

Patient Advocacy Groups

- American Cancer Society
- American Lung Association
- Bonnie J. Addario Lung Cancer Foundation (ALCF)
- Cancer Leadership Council
- Cancer Research and Prevention Foundation
- Caring Ambassadors Lung Cancer Program
- Dusty Joy Foundation
- EX: Re-learn Live without Cigarettes
- Free Me From Lung Cancer
- Free to Breathe
- Global Lung Cancer Coalition
- Global Resource for Advancing Cancer Education
- International Thoracic Oncology Nursing Forum
- Lung Cancer Alliance
- Lung Cancer Foundation of American (LCFA)
- Lung Cancer Research Foundation (LCRF)
- Lungevity Foundation
- Mesothelioma Applied Research Foundation
- My Cancer Genome
- Partnership Against Cancer American Cancer Society
- Prevent Cancer Foundation
- Roy Castle Lung Cancer Foundation
- UICC Global Cancer Control Community
- Union for International Cancer Control
- Uniting Against Lung Cancer
- Women Against Lung Cancer in Europe

Government and other stakeholders:

- Centers for Disease Control and Prevention (CDC)
- Centers for Medicare & Medicaid Services (CMS)
- China Food and Drug Administration
- European Medicines Agency
- National Institute for Health and Care Excellence (UK)
- Pharmaceuticals and Medical Devices Agency (Japan)
- US Food and Drug Administration (FDA)

- Veteran's Affairs (VA) and Department of Defense (DOD)

The website received 6,662 comments in total (Agree and Disagree responses were also captured). All 2013 recommendation statements achieved between 94% to 98% agreement. All 20 new draft statements achieved between 78% to 97% agreement. Teams of 3 to 4 EP members were assigned 3 to 5 draft recommendations for which to review all comments received and provide an overall summary to the rest of the panel. Following panel discussion, and the final quality of evidence assessment, the EP members determined whether to maintain the original draft recommendation as is, revise it with minor language change, or consider it as a major recommendation change. The recommendation statement about the use of mutation-specific IHC for EGFR testing when tissue is limited or insufficient was deliberated. Due to a low public consensus, and the overall utility of the method, the panel decided that the statement is not feasible for laboratories to implement. Furthermore, two draft statements about *ERBB2 (HER2)* were merged for clarity and consistency with the other statements. Resolution of all changes was obtained by majority consensus of the panel using nominal group technique (rounds of email discussion and multiple edited recommendations) amongst the panel members. The final 18 recommendation statements were approved by the EP with a formal vote. The EP considered the risks and benefits throughout the whole process in their considered judgment process. Formal cost analysis or cost effectiveness was not performed.

Organizational review was instituted to review and approve the guideline. For the CAP, an independent review panel (IRP) representing the Council on Scientific Affairs was nominated to review and approve the guideline. The IRP was masked to the EP and vetted through a COI process. The IASLC approval process required the review and approval by the IASLC Board of Directors. The AMP approval process required content review by an independent subject matter expert panel, led by the Publications & Communications Chair with representation from the Clinical Practice Committee and Solid Tumors Subdivision Leadership, and organizational approval by the AMP Executive Committee.

Dissemination Plans

Final dissemination of the guideline will be a joint process between the three organizations. There are plans to host a resource page which will include a link to the manuscript and supplement, summary of the recommendations, social media posts and email blasts, as well as patient information guides. The guideline will be promoted and presented at various society meetings.

Systematic Evidence Review (SER)

The objective of the SER was to develop an evidence-based guideline to help establish standard molecular marker testing, guide targeted therapies, and advance personalized care for patients. If of sufficient quality, findings from this review could provide an evidence base to support the development of the guideline. The scope of the SER and the key questions (KQs) were established by the EP in consultation with the methodologist prior to beginning the literature search.

Search and Selection

A comprehensive literature search was completed to both identify new evidence to assess the original 2013 recommendations and to identify evidence that addressed the new key questions.

To assess the original 2013 recommendations, the search strategy utilized in the original guideline was run in Ovid MEDLINE (Ovid Technologies Inc., New York, NY) on 5/17/2015. Search terms included the following Medical Subject Headings (MeSH) and keywords: lung neoplasms; lung cancer; carcinoma, non-small cell lung; EGFR; epidermal growth factor receptor; ALK; KRAS; BRAF; mutation; amplification; gene copy number; rearrangement; fusion; translocation; inversion; immunohistochemistry; IHC; and FISH. Studies published in English

with publication dates from 1/01/2012 to 5/17/2015 were included, and a publication filter was applied to identify medical practice guidelines, systematic reviews, meta-analyses, and randomized clinical trials. EP recommendations supplemented the literature search, and the Ovid search was rerun on 6/27/16 to identify relevant new literature published between 4/01/2015 and 6/27/2016.

A second literature search was designed to gather evidence in order to answer key questions new to this project and inform new recommendations based on those questions. This search involved different literature strategies for each main key question with limits set based on input from the project co-chairs. The first search strategy addressed key question 1 (subquestions I-VII) that focuses on new biomarkers in lung cancer, and it was performed in Ovid MEDLINE on 5/21/2015, and a supplemental search was run in PubMed (U.S. National Library of Medicine, Bethesda, MD) on 6/28/2015. The search combined MeSH terms and keywords to address the concepts lung cancer (non-small cell lung cancer (NSCLC)/Adenocarcinoma), new biomarkers not addressed by the 2013 guideline, targeted therapy, treatment outcomes, laboratory testing methods and test outcomes or patient characteristics. The search was limited to English language studies published between 1/01/2007 and 5/21/2015 (Ovid) or 1/01/2007 and 6/28/2015 (PubMed). Publication types were limited to practice guidelines and consensus statements, systematic reviews, meta-analyses, clinical trials, and observational studies. Low level evidence such as letters, editorials, commentaries, and case reports were excluded.

The search strategy designed to answer key question 2 that addresses Anaplastic Lymphoma Kinase (ALK) testing combined MeSH terms and keywords for the concepts lung cancer (NSCLC/Adenocarcinoma), ALK, laboratory testing methodologies, and test outcomes or patient characteristics. The search was performed in Ovid MEDLINE on 5/21/2015, and a supplemental search was run in PubMed on 6/28/2015. Both searches were limited to English language studies published between 1/01/2012 and 5/21/2015 (Ovid) or 1/01/2012 and 6/28/2015 (PubMed). Publication types were limited to practice guidelines and consensus statements, systematic reviews, meta-analyses, clinical trials, and observational studies. Low level evidence such as letters, editorials, commentaries, and case reports were excluded.

The search strategy designed to address key question 3 relating to secondary resistance combined MeSH terms and keywords for the concepts lung cancer (NSCLC/adenocarcinoma), biomarkers, targeted therapy and secondary resistance. The search was performed in Ovid MEDLINE (5/21/2015) and PubMed (6/28/2015) and was limited to English language studies published between 1/01/2012 and 5/21/2015 (Ovid) or 1/01/2012 and 6/28/2015 (PubMed). All publication types were initially included due to concern over limited available evidence.

The search strategy to address key question 4 related to biomarker testing in squamous and small cell lung carcinomas combined MeSH and keywords to address the concepts of “squamous or small cell carcinoma of the lung”, “lung cancer treatment”, “biomarkers”, “treatment outcomes. The search was performed in Ovid MEDLINE (5/21/15) and PubMed (6/28/15) interfaces and was limited to English language studies published between 1/01/2011 and 5/21/15 (Ovid) or 1/01/2011 and 6/28/15 (PubMed). Publication types were limited to practice guidelines and consensus statements, systematic reviews, meta-analyses, clinical trials, and observational studies. Low level evidence such as letters, editorials, commentaries, and case reports were excluded.

The search strategy to address key question 5 relating to the use of circulating DNA/ CTCs for the diagnosis of primary or recurrent lung cancer combined MeSH and keywords for the concepts lung cancer (NSCLC/adenocarcinoma), biomarkers, circulating dna/circulating tumor cells, and testing outcomes. The search was performed in Ovid MEDLINE on 5/21/2015, and a supplemental search was done utilizing PubMed on 6/28/2015. The searches were limited to English language studies published between 1/01/2012 and 5/21/2015 (Ovid) or 1/01/2012 and

6/28/2015 (PubMed). Publication types were limited to practice guidelines and consensus statements, systematic reviews, meta-analyses, clinical trials, and observational studies. Low level evidence such as letters, editorials, commentaries, and case reports were excluded.

A supplemental search for each key question was adapted from the Ovid MEDLINE search strategy and run in Scopus (Elsevier Inc., Atlanta, GA) on 6/25/2015 to identify publications not indexed in MEDLINE. Publication date limits were set based on the parameters described above, with the end date of 6/25/2015 for all searches.

A search for clinical trials was completed on 7/13/2015 using the clinicaltrials.gov website to identify published or unpublished study results for trials indexed with the conditions “lung cancer” or “lung neoplasms” and the following keywords: biomarker, ALK, BRAF, KRAS, cMET, EGFR, ERBB2, HER2, MET, or RET.

Additional searches were performed to identify relevant practice guidelines or unpublished (“gray”) literature. Focused searches of guideline and systematic review repositories (e.g., Prospero, National Institute for Health and Care Excellence [NICE], guidelines.gov, Guidelines International Network [g-i-n.net]) and relevant organization’s websites (e.g., NCCN, ASCO, Cancer Care Ontario) were completed to identify documents related to biomarker testing in lung cancer. EP recommendations completed the systematic literature review. All Ovid MEDLINE searches were rerun on 6/27/16 to identify any relevant new literature published from 4/01/15 to 6/27/16.

All Ovid search strings are included as Appendix 1. The PRISMA charts detailing the systematic reviews for each aspect of the project are included as Supplement Figure 1 and 2.

Selection at all levels was based on predetermined inclusion/exclusion criteria.

Inclusion Criteria

1) Studies must either:
    a. Prospectively or retrospectively evaluate the sensitivity, specificity, negative predictive value, or positive predictive value of *EGFR*, *ALK*, *KRAS, ROS1*, *RET*, *MET*, *BRAF*, or *ERBB2(HER2)* tests for detection of gene-specific mutation, rearrangement, translocation, amplification or overexpression, or response to a targeted gene-specific therapy.
    b. Examine potential testing algorithms for NSCLC molecular testing
    c. Examine the correlation of *EGFR*, *ALK*, *KRAS*, *ROS1*, *RET*, *MET*, *BRAF*, or *ERBB2(HER2)* status in primary or metastatic tumors from the same patients
2) Study population must consist of patients with a diagnosis of adenocarcinoma, NSCLC, SCLC, squamous cell lung cancer, or non-squamous cell lung cancer of any stage as specified by each key question.
3) Studies must include as primary outcomes:
    a. Sensitivity, specificity, positive predictive value, and negative predictive value of tests to determine *EGFR*, *ALK*, *KRAS*, *ROS1*, *RET*, *MET*, *BRAF*, or *ERBB2(HER2)* status or treatment response, alone or in combination OR
    b. Concordance across platforms OR
    c. Accuracy in determining *EGFR*, *ALK*, *KRAS*, *ROS1*, *RET*, *MET*, *BRAF*, or *ERBB2(HER2)* status and benefit from targeted therapy
4) Peer-reviewed full-text articles

Exclusion Criteria

1) Letters
2) Commentaries
3) Editorials

4) Reviews
5) Case reports
6) Studies in mouse models
7) In vitro studies
8) Consensus documents
9) Articles not in the English language
10) Meeting abstracts

Outcomes of Interest

The primary outcomes of interest included patient characteristics, clinical outcomes, and performance characteristics of laboratory testing assays. Patient and clinical characteristics included: age, sex, ethnicity, smoking status, stage of disease, tumor differentiation, and biomarker status. Clinical outcomes included survival rates (overall survival [OS], disease-free survival [DFS], progression free survival [PFS], recurrence-free survival [RFS], time to recurrence) and treatment response rates (complete and partial response). Laboratory test performance characteristics included: accuracy, sensitivity and specificity, sensitivity limit/analytic sensitivity, positive predictive value, negative predictive value, concordance across testing platforms, and spectrum and/or percent of mutations detected.

Data Extraction & Management

Dual study selection and data extraction were completed using systematic review database software (DistillerSR, Evidence Partners, Ottawa, Canada). Following the initial search, citations identified to assess the need for refinement of the original 2013 guideline statements were uploaded into one DistillerSR project (Lung Cancer – original) and citations identified to address the new key questions were uploaded into a second DistillerSR project (Lung Cancer – new). For the Lung Cancer – original project, co-chairs performed dual review of title and abstracts to determine if identified studies would change the 2013 guideline statements. Conflicts were flagged in DistillerSR and resolved by the co-chairs. Studies that passed title and abstract review underwent full text review by a methodologist to determine compliance to the study selection criteria. For the Lung Cancer – new project, EP members were partnered with a methodologist for dual title and abstract review to determine relevancy. Conflicts were flagged in DistillerSR and resolved through discussion by initial reviewers and further adjudicated by a project co-chair, if necessary. Those deemed relevant to the key questions that met inclusion criteria and none of the exclusion criteria were moved on to full text review. Full text articles were reviewed for relevancy by two EP members to determine eligibility, and conflicts were resolved by the initial reviewers and further adjudicated by a project co-chair, if necessary. A second level full text review was conducted by a methodologist to ensure all included studies contained complete and useable extractable data and to exclude any primary studies that were already included within the reference list of an included systematic review. In cases of duplication of reporting study results, the most inclusive were retained. Data elements from included studies were extracted by a methodologist into predesigned data extraction forms developed using DistillerSR and EP members audited the forms for both projects. Any discrepancies in data extraction were resolved by discussion. A bibliographic database was established in EndNote (Thomson Reuters, Carlsbad, CA) to track all literature identified and reviewed during the study.

Meta-Analyses of Test Accuracy Studies Methods

Meta-analyses of test accuracy studies were performed when identified studies demonstrated homogeneity of population, methods, and outcome definition and when the panel agreed that a pooled estimate statistic would aid in developing a recommendation. For each study included in a meta-analysis, true positive, true negative, false positive, and false negative data based on concordance between the index test and the reference standard were extracted and imported into both RevMan[4] to generate forest plots and imported into StataMP v14 (StataCorp, College Station, TX) to perform the meta-analyses. The pooled estimates of sensitivity and specificity

and their 95% confidence intervals were modelled using the *metandi* module[5, 6] in StataMP v14. *Metandi* performs bivariate meta-analyses of sensitivity and specificity using a generalized linear mixed model approach.[7]

Quality Assessment Methods

An assessment of the quality of the evidence was performed for all retained studies following application of the inclusion and exclusion criteria. Using this method, studies deemed to be of low quality would not be excluded from the systematic review, but would be retained and their methodological strengths and weaknesses discussed where relevant. To define an overall study quality rating for each included study, validated study-type specific tools were used to assess the risk of bias, plus additional important quality features were extracted. Specific details for each study type are outlined below.

Systematic Reviews (SRs) and Meta-Analyses (MAs)

- The following questions were assessed as per the Assessing the Methodological Quality of Systematic Reviews (AMSTAR)[8] tool using Yes or No:
  1. Was an 'a priori' design provided?
  2. Was there duplicate study selection and data extraction?
  3. Was a comprehensive literature search performed?
  4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
  5. Was a list of studies (included and excluded) provided?
  6. Were the characteristics of the included studies provided?
  7. Was the scientific quality of the included studies assessed and documented?
  8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
  9. Were the methods used to combine the findings of studies appropriate?
  10. Was the likelihood of publication bias assessed?
  11. Was the conflict of interest included?
- Additional assessed items included and were assessed as Yes, No, or Unclear:
  1. If MA was based on a SR (assessed for MAs only)
  2. Reporting of funding sources.

Randomized Control Trials (RCTs)

- The following domains were assessed using the Cochrane Risk of Bias tool[9] using low risk, unclear risk, and high risk:
  1. Random sequence generation (selection bias)
  2. Allocation concealment (selection bias)
  3. Blinding of participants and personnel (performance bias)
  4. Blinding of outcome assessment (detection bias – patient-reported outcomes)
  5. Incomplete outcome data (attrition bias)
  6. Selective outcome reporting (reporting bias)
  7. Other potential threats to validity
- Additional assessed items included and were assessed as Yes, No, Unclear:
  1. Validated and reliable measures
  2. Adequate follow-up
  3. Intention-to-Treat analysis
  4. Adequately powered
  5. Adequately powered subgroup analysis (if included)
  6. Conflict of interest reported

Single-arm non-randomized phase I and II clinical trials (NRCTs), prospective cohort studies (PCS), prospective-retrospective cohort studies (PRCS), retrospective cohort studies (RCS), and case-control studies (CCS)

- A simplified version of the Risk of Bias in Non-randomized Studies of Intervention (ROBINs-I) tool[10] was used to assess for the presence of the following types of bias in NRCTs and PCSs using Yes, No, Unclear:
    1. Selection bias
    2. Misclassification bias
    3. Attrition bias
    4. Recall bias
2. Additional assessed items for NRCT, PCS, PRCS, RCS, and CCS included and were assessed as Yes, No, Unclear:
    1. Balance between treatment/assessment groups
    2. Reporting of baseline characteristics
    3. Reporting if any adjustments were made where baseline differences were detected
    4. Sources of funding

The strength of evidence informing each key question was based on the aggregate quality of the studies identified to inform that key question.

Assessing the Strength of Recommendations

The overarching goals of the EP were to review and affirm or update the 2013 guideline recommendations, and to determine if there was additional new evidence to help establish standard molecular marker testing, guide targeted therapies, and advance personalized care for patients.
Development of recommendations required that the panel review the identified evidence and make a series of key judgments:

1) What are the significant findings related to each KQ or outcome? Determine any regulatory requirements and/or evidence that support a specific action.
2) What is the overall strength of evidence supporting each KQ or outcome? Strength of evidence is graded as convincing, adequate, inadequate, or insufficient based on our confidence in the estimate of effect reported by the included studies (Supplemental Table 1). Strength of evidence is a key element in determining the strength of a recommendation.
3) What is the strength of each recommendation? There are many methods for determining the strength of a recommendation based on the strength of evidence and the magnitude of net benefit or harm (Supplemental Table 2). Recommendations not supported by evidence (i.e., evidence was missing or insufficient to permit a conclusion to be reached) were made based on consensus expert opinion. Another potential consideration is the likelihood that additional studies will be conducted that fill gaps in knowledge.
4) What is the net balance of benefits and harms? The consideration of net balance of benefits and harms will focus on the recommendation that should be adopted as a standard in the molecular testing for lung cancer.

Considered Judgement

In addition to the panel discussion of the net benefits and harms for each guideline statement, the EP members rated each recommendation using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence-to-decision framework (Table 3). This allows for a systematic way to document panel members' judgement for each of the recommendations.[11]

For each statement, a series of judgements were rated by the panel members:

1. Benefits and Harms
    - Are the desirable anticipated effects large?
    - Are the undesirable anticipated effects small?
    - Are the desirable effects large relative to undesirable effects?
2. Resources Required:

- Are the resources required small?

3. Feasibility
   - Is the option (or recommendation) feasible to implement?
4. Acceptability:
   - Is the option acceptable to key stakeholders?

Articulation of Recommendations

In order to articulate recommendation statements that were clearly written and easy to implement, the EP employed GLIDES (Guidelines Into Decision Support) methodology and accompanying BridgeWiz software (Yale University, New Haven, CT).[12] This methodology prioritizes the use of active language; however, in some situations, the person responsible for ensuring guidance is implemented is dependent on the organization of the clinic and/or laboratory. To ensure clarity of guidance in these situations, the EP employed passive voice language to emphasize the recommended action. This guideline uses a three-tier system to rate the strength of recommendations, as well as a "No Recommendation" category when there is insufficient evidence to support a recommendation. Supplement Table 2 summarizes the level of evidence and net benefits and harms, as well as obligatory language that was used for each of the recommendation types.

When the 2013 guideline recommendations were published, an older rating system for establishing the strength of recommendations was used. In order to ensure the reaffirmed 2013 recommendation statements were aligned with the rating system used for the newly crafted recommendations, the quality assessment tables and balance of benefits and harms from the original guideline were reviewed and each recommendation statement was translated into the strength of evidence grades used in the current guideline (Supplemental Table 1). Additionally, when applicable, following the Institute of Medicine's *Clinical Practice Guidelines We Can Trust* standards,[13] the 2013 statements were rewritten into standardized actionable statements with details on what needs to be done by whom.

Supplemental Table 4a compares the strength of recommendation rating system for the 2013 recommendation statements with the 2018 recommendation statements. Supplemental Table 4b includes a list of statements with updated ratings of the strength of recommendations, as well as the list of the reaffirmed statements rewritten using the GLIDES program to reflect standardized actionable statements with details on what needs to be done by whom.

Quality Assessment Results

A total of 140 studies[14-153] were retained; 119 studies[14-130, 152, 153] formed the evidence base for the new key questions (Lung Cancer – new) and 21 were identified[131-151] as studies that could lead to refinement of the original guideline statements (Lung Cancer – original). For the Lung Cancer - original project, the 21 studies were comprised of 14 SRs[131-144] and seven RCTs.[145-151] For the Lung Cancer – new project, the 119 studies included nine MAs[26, 34, 35, 41, 64, 92, 123-125], two RCTs,[47, 73] six NRCTs,[45, 70, 75, 126, 128, 129] 35 PCS,[24, 27, 30-33, 40, 42, 49-52, 54, 55, 57, 66, 69, 79, 82, 85, 86, 88-91, 97, 102, 105, 107, 108, 120-122, 127, 130] 12 PRCS,[20, 21, 23, 25, 28, 43, 46, 59, 67, 110, 152, 153] 54 RCS,[14-19, 22, 29, 36-39, 44, 48, 53, 56, 58, 60-63, 65, 68, 71, 72, 74, 76, 78, 80, 81, 83, 84, 87, 93-96, 98-101, 103, 104, 106, 109, 111-119] and one CCS.[77] All included studies were assessed for quality.

The SER did not identify any studies that directly addressed KQ1-VII. For clarity in the guideline, the EP has discussed the need for technical validation experiments for each biomarker within the section for that biomarker. There is no recommendation statement to inform KQ1-VII.

GUIDELINE STATEMENTS

REAFFIRMED 2013 RECOMMENDATION STATEMENTS

Recommendation: Physicians should use molecular testing for the appropriate genetic targets on either primary or metastatic lung lesions to guide initial therapy selection.
One new MA[141] was identified to support this 2013 recommendation. The MA was assessed as high quality and was only limited by a lack of conflict of interest declaration. Refer to Supplement Table 5 for the quality assessment results of new studies informing this recommendation. This recommendation statement has been reaffirmed by new evidence.

Strong Recommendation: Laboratories should not use total EGFR expression by IHC testing to select patients for EGFR-targeted tyrosine kinase inhibitor therapy.
One new MA[132] was identified to support this 2013 recommendation. The MA was assessed as high quality and only suffered from status of publication not having been used as an inclusion criterion for the SR. Refer to Supplement Table 5 for the quality assessment results of new studies reaffirming this recommendation. This recommendation statement has been reaffirmed and has increased in strength from a Recommendation to a Strong Recommendation based on the newly identified evidence.

Recommendation: Pathologists and laboratories should not use *EGFR* copy number analysis (i.e., FISH or chromogenic in situ hybridization [CISH]) to select patients for EGFR-targeted tyrosine kinase inhibitor therapy.
One phase II single-arm NRCT[154] that could refute the original recommendation statement was identified. The phase II study was assessed as intermediate based on the single-arm design, presence of selection bias, and unclear reporting of the balance between assessment groups. Refer to Supplement Table 5 for the quality assessment results of new studies informing this recommendation. After review of the study, the EP believed that this single study was an outlier and the guideline statement was reaffirmed.

UPDATED 2013 RECOMMENDATION STATEMENTS

Expert consensus opinion: Pathologists may utilize either cell blocks or other cytologic preparations as suitable specimens for lung cancer biomarker molecular testing.
The 2013 recommendation statement preferred cell blocks over smears. This recommendation was reaffirmed with the addition of one SR[133]. The SR was assessed as intermediate quality based on status of publication not having been used as an inclusion criterion, lack of a list of studies included and excluded, no publication bias assessment and no conflict of interest declaration included. Refer to Supplement Table 5 for the quality assessment results of new studies informing this recommendation. The systematic review indicated that numerous published studies have more recently shown excellent performance of smear preparations. The evidence leads the EP to alter the statement to allow the use of cytologic preparations. Laboratories that test cytology specimens must still perform the appropriate validation studies of these sample types, distinct from tissue and blood samples.

Expert consensus opinion: Laboratories should employ, or have available at an external reference laboratory, clinical lung cancer biomarker molecular testing assays that are able to detect molecular alterations in specimens with as little as 20% cancer cells.
The 2013 recommendation statement recommended that laboratories use an EGFR test method able to detect mutations in specimens with at least 50% cancer cell content. Laboratories were strongly encouraged to employ a more sensitive method with the ability to detect mutations in specimens with as little as 10% cancer cells. After three years in practice, it is now the opinion of the EP that the original recommendation was insufficient. There is now widespread availability of technologies capable of reliably detecting lower frequency mutational events in small samples, reducing the potential for additional or invasive procedures in patients to procure a sample with high tumor content. The EP believes it is now appropriate for laboratories to employ an assay with a higher sensitivity.

NEW RECOMMENDATION STATEMENTS

Key Question 1: Which new genes should be tested for lung cancer patients?

ROS1

1. **Strong Recommendation: *ROS1* testing must be performed on all advanced stage lung adenocarcinoma patients, irrespective of clinical characteristics.**
This recommendation was supported by nine studies,[17, 25, 39, 45, 84, 88, 94, 106, 111] six of which informed on the association between *ROS1* mutation and patient or tumor characteristics[17, 25, 84, 88, 94, 106] and three studies which examined patients treated with crizotinib.[39, 45, 111] Of the nine studies, there was one single-arm phase I NRCT,[45] one PCS,[88] one PRCS,[25] and six RCSs.[17, 39, 84, 94, 106, 111] Of the studies that examined the association of *ROS1* mutation and patient or tumor characteristics, the PCS[88] was of intermediate quality and the PRCS[25] was of intermediate-low quality. The remaining four studies were RCS and all assessed as low quality. The single-arm phase I NRCT[45] that assessed patients with *ROS1* mutation treated with crizotinib was assessed as intermediate quality based on its non-comparative design and both selection and recall bias limitations. The two RCS that assessed treatment with crizotinib in this population were low and very low quality. Overall, none of the studies informing the evidence base for Statement 1 were found to have methodological flaws that would raise concerns about the studies' finding. Refer to Supplement Table 6 for the quality assessment results of studies informing Statement 1. A summary of findings supporting the use of testing for ROS1 alterations can be found in Supplemental Table 7.

   Supplemental Table 3 summarizes the evidence-to-decision ratings for Statement 1. Given the excellent response to ROS1 tyrosine kinase inhibitors (TKIs) and little to no undesirable effects, the EP believes that the benefits of testing for *ROS1* alteration outweigh any harm. The resources required to implement this recommendation will vary based on whether FISH, IHC, PCR or NGS testing is being performed, but the EP believes the recommendation is feasible.

2. **Expert Consensus Opinion: ROS1 IHC may be used as a screening test in advanced stage lung adenocarcinoma patients; however, positive ROS1 IHC results should be confirmed by a molecular or cytogenetic method.**
This recommendation was supported by eight studies[23, 42, 86, 88, 94, 96, 99, 112] comprised of three PCSs,[42, 86, 88] one PRCS,[23] and four RCSs.[94, 96, 99, 112] The three PCS studies were assessed as intermediate (n=1) and intermediate-low (n=2) with the two lesser quality PCSs suffering from selection bias in one and attrition bias in the other. The one PRCS and four RCS were assessed as low (n=4) and very low (n=1) based on retrospective analysis of data and a lack of reporting baseline characteristics of enrolled patients across all five studies. Overall, none of the studies informing the evidence base for Statement 2 were found to have methodological flaws that would raise concerns about the studies' finding. Refer to Supplement Table 8 for the quality assessment results of studies informing Statement 2. A summary of findings supporting the use of IHC screening for ROS1 alteration can be found in Supplemental Table 9.

   Supplemental Table 3 summarizes the evidence-to-decision ratings for Statement 2. IHC performance for ROS1 alteration identification is evolving. The desirable effects of quickly determining tumors that are negative for ROS1 alteration are large; however, IHC testing does carry a chance for false positive tests, thus leading to a need for confirmation testing. The EP believes this recommendation is feasible and acceptable to stakeholders with a small resource requirement.

BRAF

3. Expert Consensus Opinion: *BRAF* molecular testing is currently not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *BRAF* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.

This expert consensus opinion was supported by nine studies, seven of which informed on the association between *BRAF* mutation and patient or tumor characteristics[22, 27, 31-33, 36, 119] and two which assessed the activity of a BRAF inhibitor.[128, 129] Of the nine studies, there were two single-arm phase II NRCTs,[128, 129] four PCS,[27, 31-33] and three RCSs.[22, 36, 119] Two single-arm phase II NRCTs[128, 129] that assessed the activity of a BRAF inhibitor in patients with *BRAF* mutation were assessed as intermediate-low quality. The studies were conducted by the same research group and were companion studies, both suffering from selection bias. Of the seven studies that examined the association between *BRAF* mutation status and patient or tumor characteristics, the PCS were assessed as intermediate (n=1), intermediate-low (n=2), and low (n=1) quality, while the three RCS were assessed as low (n=2) and very low (n=1). Limitations of the observational studies included a lack of reporting on baseline characteristics of patients (n=3), unclear reporting of the balance between groups of compared patients (n=4), and recall bias (n=1). Overall, none of the studies informing the evidence base for Statement 3 were found to have methodological flaws that would raise concerns about the studies' finding. Refer to Supplement Table 10 for the quality assessment results of studies informing Statement 3. Studies that support the use of *BRAF* molecular testing are summarized in Supplemental Table 11.

Supplemental Table 3 summarizes the evidence-to-decision ratings for Statement 3. Given the lack of randomized evidence supporting any benefit to testing for *BRAF* in this population, the EP is split on whether the desirable anticipated effects of *BRAF* molecular testing are large and whether the undesirable effects are small. However, addition of *BRAF* to a larger NGS gene panel requires minimal resources, making this recommendation feasible to implement.

RET

4. Expert Consensus Opinion: *RET* molecular testing is not recommended as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *RET* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.

This expert consensus opinion was supported by three studies,[82, 106, 115] comprised of one PCS[82] and two RCS.[106, 115] The PCS was assessed as intermediate-low quality and the RCS were both assessed as low quality. Overall, none of the studies informing the evidence base for Statement 4 were found to have methodological flaws that would raise concerns about the studies' finding. Refer to Supplement Table 12 for the quality assessment results of studies informing Statement 4. A summary of findings supporting the use of *RET* molecular testing can be found in Supplemental Table 13.

Supplemental Table 3 summarizes the evidence-to-decision ratings for Statement 4. Given the lack of randomized evidence supporting any benefit to testing for *RET* in this population, the EP is split on whether the desirable anticipated effects of *RET* are large. Additionally, due to the lack of clinical data, the EP is split on the potential for undesirable anticipated effects. However, addition of *RET* to a larger NGS gene panel requires minimal resources and the EP believes that the recommendation is feasible to implement.

ERBB2 (HER2)

5. Expert Consensus Opinion: *ERBB2 (HER2)* molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *ERBB2 (HER2)* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.

This expert consensus opinion was supported by 10 studies, nine of which informed on the association between *ERBB2 (HER2)* and patient or tumor characteristics[14, 19, 27, 34, 80, 81, 97, 113, 114] and one study which assessed the use of ERBB2-targeted therapy.[126] Of the total 10 studies, there was one MA,[34] one single-arm phase II NRCT,[126] two PCS,[27, 97] and six RCS.[14, 19, 80, 81, 113, 114] Of the nine studies which examined the association between *ERBB2* mutation status and patient or tumor characteristics, the PCS were assessed as intermediate (n=1) and intermediate-low (n=1), while the RCS were assessed as low (n=4) or very low quality (n=2). These observational studies were limited by a lack of balance between assessment groups when studies were comparative (n=5) and a lack of reporting of baseline characteristic (n=2). The single-arm phase II NRCT[126] that assessed the use of ERBB2-targeted therapy in an *ERBB2* mutation positive population was assessed as intermediate quality and was limited by its single-arm design, as well as selection and recall bias. Overall, none of the studies informing the evidence base for Statement 5 were found to have methodological flaws that would raise concerns about the studies' finding. Refer to Supplement Table 14 for the quality assessment results of studies informing Statement 5. Findings from studies that evaluated the use of *ERBB2 (HER2)* molecular testing in a lung cancer population are summarized in Supplemental Table 15.

Supplemental Table 3 summarizes the evidence-to-decision ratings for Statement 5. The EP is split between believing the desirable anticipated effects of conducting *ERBB2 (HER2)* testing are probably small and being uncertain. However, based on the available evidence, the EP also believes that there are little to no harms to testing and that the addition of *ERBB2 (HER2)* to a larger NGS gene panel would require minimal resources. Thus, the EP believes that the recommendation is feasible to implement.

KRAS

6. Expert Consensus Opinion: *KRAS* molecular testing is not indicated as a routine stand-alone assay as a sole determinant of targeted therapy. It is appropriate to include *KRAS* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.

This statement was supported by seven studies,[24, 27, 32, 33, 35, 41, 117] comprised of two MAs,[35, 41] four PCS,[24, 27, 32, 33] and one RCS.[117] The MAs were assessed as high[41] and high-intermediate[35] quality. The lesser quality MA did not assess the quality of the included studies and thus the quality of the studies was not considered when formulating conclusions. The observational studies were assessed as intermediate (n=1), intermediate-low (n=2) and low quality (n=2) based on study design and either a lack of reporting (n=1) or unclear reporting (n=3) of the balance between compared groups. Overall, none of the studies informing the evidence base for Statement 6 were found to have methodological flaws that would raise concerns about the studies' finding. Refer to Supplement Table 16 for the quality assessment results of studies informing Statement 6. Findings from studies that assessed the association between *KRAS* mutation and patient or tumor characteristics and studies that evaluated the clinical outcomes of patients positive for *KRAS* mutation are both summarized in Supplemental Table 17.

Refer to Supplemental Table 3 for the evidence-to-decision ratings for Statement 6. The EP believes that the benefits of *KRAS* molecular testing are small as there is currently no available targeted therapy for the mutation. However, the harms of testing for *KRAS* mutation are also small and the addition of *KRAS* to an NGS panel would require limited resources. The EP believes that this recommendation is feasible to implement.

MET

7. Expert Consensus Opinion: *MET* molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *MET* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.

Statement 7 was supported by seven studies,[26, 29, 47, 91, 103, 109, 116] comprised of one MA,[26] one phase II RCT,[47] one PCS,[91] and four RCSs.[29, 103, 109, 116] The MA was assessed as high quality, while the phase II RCT was assessed as high-intermediate quality and was only limited by unclear risk of performance bias and detection bias, plus incomplete outcome data reporting. The five observational studies were assessed as intermediate (n=1) and low quality (n=4) based on the study design. Overall, none of the studies informing the evidence base for Statement 7 were found to have methodological flaws that would raise concerns about the studies' finding. Refer to Supplement Table 18 for the quality assessment results of studies informing Statement 7. Supplemental Table 19 provides a summary of findings for studies that assessed the use of *MET* molecular testing.

Supplemental Table 3 summarizes the evidence-to-decision ratings for Statement 7. Due to a lack of clinical data, the EP is split on the degree of benefits and harms for *MET* molecular testing. The EP is also split on the amount of resources that would be required to implement testing. However, if *MET* molecular testing is added to a NGS panel, the EP believes the recommendation is feasible and acceptable.

Key Question 2. What methods should be used to perform molecular testing?

8. Recommendation: Immunohistochemistry (IHC) is an equivalent alternative to FISH for ALK testing.

This statement was supported by 20 studies,[40, 46, 51, 54-56, 58, 59, 61, 62, 83, 87, 93, 98, 101-103, 105, 110, 118] comprised of six PCSs,[40, 51, 54, 55, 102, 105] three PRCSs,[46, 59, 110] and 11 RCSs.[56, 58, 61, 62, 83, 87, 93, 98, 101, 103, 118] The six PCS studies that informed this statement were assessed as intermediate (n=1), intermediate-low (n=2) and low (n=3) quality based on presence of selection bias (n=4), attrition bias (n=2), and recall bias (n=1), as well as imbalance between assessment groups (n=2), lack of reporting baseline characteristics for enrolled patients (n=3), lack of reporting of adjustments where there were differences between assessment groups (n=4), and a lack of funding being reported (n=4). The three PCSC and 11 RCS were assessed as intermediate (n=1), intermediate-low (n=2), low (n=10) and very low quality (n=1) based on retrospective analysis of data in all studies, imbalance between assessment groups (n=3), lack of reporting baseline characteristics for enrolled patients (n=8), lack of reporting of adjustments where there were differences between groups (n=13), and a lack of funding being reported (n=4). Overall, none of the studies informing the evidence base for Statement 8 were found to have methodological flaws that would raise concerns about the studies' finding. Refer to Supplement Table 20 for the quality assessment results of studies informing Statement 8. The sensitivity, specificity, positive predictive value, and negative predictive value of IHC for ALK testing as reported by the included studies are summarized in Supplemental Table 21.

Supplemental Table 3 summarizes the evidence-to-decision ratings for Statement 8. The ability to detect ALK alteration with IHC has greatly improved and can be considered equivalent to FISH. The EP believes that the benefits of conducting IHC testing are large relative to any harms. Additionally, IHC testing is easier and cheaper than FISH for most laboratories, making this recommendation feasible to implement.

9. Expert Consensus Opinion: Multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond *EGFR*, *ALK*, and *ROS1*. Statement 9 was supported by five studies,[48, 100, 120, 152, 153] comprised of one PCSs,[120] two PRCSs,[152, 153] and two RCS.[48, 100] The PCS identified to inform this statement was assessed as intermediate-low quality and the two PRCS and two RCSs were all

assessed as low quality. Limitations of these studies included either imbalance or unclear reporting of balance between assessment groups (n=4) and lack of reporting adjustments when difference were present between assessment groups (n=6). Overall, none of the studies informing the evidence base for Statement 9 were found to have methodological flaws that would raise concerns about the studies' finding. Refer to Supplement Table 22 for the quality assessment results of studies informing Statement 9. Concordance rates, sensitivity and specificity of multiplex genetic sequencing compared with single-gene testing as reported by the identified studies are summarized in Supplemental Table 23.

Supplemental Table 3 summarizes the evidence-to-decision ratings for Statement 9. Although the benefits of multiplex testing outweigh the limited harms, there was considerable discussion among the EP surrounding the resources, acceptability, and feasibility of implementing this recommendation. The resources involved in moving away from single-gene testing may be large for some organizations and this will greatly impact the feasibility in these settings. The acceptability of this recommendation varies based on the stakeholder. Although it is anticipated that oncologists and patients will find a move to multiplex testing acceptable, it may be unacceptable for payers and for laboratories that cannot afford to make the switch,

10. **Expert Consensus Opinion: Laboratories should ensure test results that are unexpected, discordant, equivocal, or otherwise of low confidence be confirmed or resolved using an alternative method or sample.**
No studies were identified by the systematic review to inform Statement 10.

Although this statement is based solely on the consensus opinion of the EP, there was unanimous agreement among the EP that implementation of this recommendation will positively impact patient care and implementation is feasible.

Key Question 3: Is molecular testing appropriate for lung cancers that do not have an adenocarcinoma component?

11. **Expert Consensus Opinion: Physicians may use molecular biomarker testing in tumors with histologies other than adenocarcinoma when clinical features indicate a higher probability of an oncogenic driver.**
No studies were identified by the systematic review to inform Statement 11.

Supplemental Table 3 summarizes the evidence-to-decision ratings for Statement 11. Although this recommendation is based solely on the consensus opinion of the EP, finding ways to not exclude patients from testing is desirable and thus, the benefits of implementing this recommendation outweigh any harms. Additionally, the required resources will be small and not substantially different from the current standard of care. The EP believes that implementing of this recommendation is feasible.

Key Question 4: What testing is indicated for patients with targetable mutations who have relapsed on targeted therapy?

12. **Strong Recommendation: In lung adenocarcinoma patients who harbor sensitizing *EGFR* mutations and have progressed after treatment with an EGFR-targeted tyrosine kinase inhibitor, *EGFR* T790M mutational testing should be used to guide selection of treatment with third generation EGFR inhibitors.**

This recommendation was supported by five studies,[65, 69, 70, 75, 124] including one MA,[124] two single arm phase I NRCTs,[70, 75] one PCS,[69] and one RCS.[65] The MA was of high quality, the single-arm phase I NRCT studies were both assessed as intermediate quality based on being non-comparative studies and one suffered from recall bias.[70] The two observational

studies[65, 69] were assessed as intermediate and low quality respectively. Overall, none of the studies informing the evidence base for this statement were found to have methodological flaws that would raise concerns about the studies' finding. Refer to Supplement Table 24 for the quality assessment results of studies informing Statement 12. A summary of findings from studies that assessed the clinical outcomes of patients with known T790M mutation following EGFR-TKI treatment are summarizes in Supplemental Table 25.

Although the EP did not perform a formal evidence-to-decision assessment for this recommendation, based on the reported response rates and disease control rates for patients with and without *EGFR* T790M mutation treated with a third generation EGFR inhibitor, there was unanimous agreement among the members that implementation of this recommendation will positively impact patient care. The EP believes that implementation of this recommendation is feasible.

13. **Recommendation: Laboratories testing for *EGFR* T790M mutation in patients with secondary clinical resistance to EGFR-targeted kinase inhibitors should deploy assays capable of detecting *EGFR* T790M mutations in as little as 5% of EGFR alleles.**
No studies were identified by the systematic review to inform Statement 13.

Although this statement is based solely on the consensus opinion of the EP, there was unanimous agreement among the EP that implementation of this recommendation will positively impact patient care and implementation is feasible.

14. **No Recommendation: There is currently insufficient evidence to support a recommendation for or against routine testing for *ALK* mutational status for lung adenocarcinoma patients with sensitizing *ALK* mutations who have progressed after treatment with an ALK-targeted tyrosine kinase inhibitor.**
No studies were identified by the systematic review to inform Statement 14.

Supplemental Table 3 summarizes the evidence-to-decision ratings for Statement 14. Based on a lack of evidence, the EP is uncertain on the balance between the benefits of testing for sensitizing *ALK* mutation testing and the harms. The EP is also split on the degree of resources that would be necessary to implement a recommendation and both the feasibility and acceptability of making a recommendation. Thus, the EP believes that no recommendation is feasible.

Key Question 5: What is the role of testing for circulating, cell-free DNA, for lung cancer patients?

15. **No Recommendation: There is currently insufficient evidence to support the use of circulating cell-free plasma DNA (cfDNA) molecular methods for the diagnosis of primary lung adenocarcinoma.**
No studies were identified by the systematic review to inform Statement 15.

Supplemental Table 3 summarizes the evidence-to-decision ratings for Statement 15. Based on a lack of evidence, the EP is split on the balance of benefits and harms, the resources required to implement a recommendation, and the acceptability of such a recommendation. At this time, a recommendation would not be feasible.

16. **Recommendation: In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cell-free plasma DNA (cfDNA) assay to identify *EGFR* mutations.**
Statement 16 was supported by six studies,[43, 67, 90, 92, 108, 125] comprised of two MAs,[92, 125] two PCSs,[90, 108] and two PRCS.[43, 67] Of the two MAs, one was assessed as high quality[92] while

the other was assessed as high-intermediate[125] based on a lack of duplicate study selection and data extraction, lack of included study characteristic reporting, and no publication bias assessment. One PCS was assessed as high-intermediate[108] and the other as intermediate-low[90] based on the study design and lack baseline reporting. The PRCSs were assessed as intermediate-low[43] and low quality[67] based on the retrospective design and lack of patient baseline characteristic reporting. Overall, none of the studies informing the evidence base for Statement 16 were found to have methodological flaws that would raise concerns about the studies' finding. Refer to Supplement Table 26 for the quality assessment results of studies informing Statement 16. Supplemental Table 27 summarizes the reported diagnostic accuracy of cfDNA compared with tumor tissue in the identified studies.

Supplemental Table 3 summarizes the evidence-to-decision ratings for Statement 16. The EP believes that the benefit of using cfDNA to identify *EGFR* mutations in this defined situation outweighs the little to no undesirable effects. Additionally, the resources to implement this recommendation are small, making this recommendation feasible.

17. **Expert Consensus Opinion: Physicians may use cell-free plasma DNA (cfDNA) methods to identify *EGFR* T790M mutations in lung adenocarcinoma patients with progression or secondary clinical resistance to EGFR-targeted tyrosine kinase inhibitors; testing of the tumor sample is recommended if the plasma result is negative.**

Statement 17 was supported by four studies,[68, 74, 127, 130] comprised of two PCSs[127, 130] and two RCSs.[68, 74] Both PCS were assessed as intermediate-low quality based on being limited by selection bias, plus imbalance between groups in one study and lack of baseline characteristic reporting in the other. Both the RCSs were assessed as low quality based on retrospective analysis of data, imbalance between groups (n=1) and lack of reporting adjustment when differences were present between assessment groups (n=2). Overall, none of the studies informing the evidence base for Statement 17 were found to have methodological flaws that would raise concerns about the studies' finding. Refer to Supplement Table 28 for the quality assessment results of studies informing Statement 17. Studies informing this recommendation reported on concordance between cfDNA and tumor tissue identification of T790M mutation, and clinical outcomes of patients following treatment with a third-generation EGFR-TKI. A summary of findings from these studies can be found in Supplemental Table 29.

Supplemental Table 3 summarizes the evidence-to-decision ratings for Statement 17. Based on the small pool of available evidence, the EP believes that the benefits of using cfDNA to identify T790M mutations outweigh the little to no undesirable effects. The EP is split on the amount of resources that will be required to implement this recommendation, but believe the recommendation to be acceptable to stakeholders and feasible.

18. **No Recommendation: There is currently insufficient evidence to support the use of circulating tumor cell (CTC) molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of *EGFR* or other mutations, or the identification of *EGFR* T790M mutations at the time of EGFR TKI-resistance.**

No studies were identified by the systematic review to inform Statement 18.

Supplemental Table 3 summarizes the evidence-to-decision ratings for Statement 18. Based on a lack of evidence, although the EP believes that the benefits of using CTC to diagnosis primary lung adenocarcinoma outweigh the anticipated harms, the EP is split on the degree of benefit that would be anticipated. Additionally, the EP remains uncertain with regards to the resources that would be required, the feasibility of implementation, and the acceptability to stakeholders.

Supplemental Table 1. Grades for Strength of Evidence

Designation	Description	Quality of Evidence
Convincing	High confidence that available evidence reflects true effect. Further research is very unlikely to change the confidence in the estimate of effect.	High/Intermediate quality evidence
Adequate	Moderate confidence that available evidence reflects true effect. Further research is likely to have an important impact on the confidence in estimate of effect and may change the estimate	Intermediate/Low quality of evidence
Inadequate	Little confidence that available evidence reflects true effect. Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.	Low/Insufficient evidence and expert panel uses formal consensus process to reach Recommendation
Insufficient	Evidence is insufficient to discern net effect. Any estimate of effect is very uncertain.	Insufficient evidence and expert panel uses formal consensus process to reach Recommendation

Adapted from *J Clin Epidemiol*, 2011;64(4), Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence, pages 401-406, copyright 2011, with permission from Elsevier.[155]

Supplemental Table 2. Grades for Strength of Recommendations

Designation	Recommendation	Rationale
Strong Recommendation	Recommend for or against a particular molecular testing practice for lung cancer (Can include “must” or “should”)	Supported by convincing (high) or adequate (intermediate) quality of evidence and clear benefit that outweighs any harms
Recommendation	Recommend for or against a particular molecular testing practice for lung cancer (Can include “should” or “may”)	Some limitations in quality of evidence (adequate [intermediate] or inadequate [low]), balance of benefits and harms, values, or costs but panel concludes that there is sufficient evidence and/or benefit to inform a recommendation
Expert Consensus Opinion	Recommend for or against a particular molecular testing practice for lung cancer (Can include “should” or “may”)	Serious limitations in quality of evidence (inadequate [low, very low] or insufficient), balance of benefits and harms, values or costs, but panel consensus is that a statement is necessary
No Recommendation	No recommendation for or against a particular molecular testing practice for lung cancer	Insufficient evidence or agreement of the balance of benefits and harms, values, or costs to provide a recommendation

Derived from Andrews et al,[156] 2013.

Supplemental Table 3. Evidence-to-Decision Ratings

	No	Probably No	Uncertain	Probably Yes	Yes	Varies
1. Strong Recommendation: *ROS1* testing must be performed on all advanced stage lung adenocarcinoma patients, irrespective of clinical characteristics.						
Benefits and Harms						
Are the desirable anticipated effects large?	✓	–	–	✓✓	✓	–
Are the undesirable anticipated effects small?	–	–	–	✓✓✓	✓	–
Are the desirable effects large relative to undesirable effects?	–	–	✓	✓✓	✓	–
Resources Required						
Are the resources required small?	–	–	✓✓✓	–	–	✓
Feasibility						
Is the option (or recommendation) feasible to implement?	–	–	✓	✓✓	✓	–
Acceptability						
Is the option acceptable to key stakeholders?	–	–	✓	–	✓✓✓	–
2. Expert Consensus Opinion: ROS1 IHC may be used as a screening test in advanced stage lung adenocarcinoma patients; however, positive ROS1 IHC results should be confirmed by a molecular or cytogenetic method.						
Benefits and Harms						
Are the desirable anticipated effects large?	–	–	–	✓✓✓	✓	–
Are the undesirable anticipated effects small?	✓	–	–	✓✓✓	–	–
Are the desirable effects large relative to undesirable effects?	–	–	✓	✓	✓✓	–
Resources Required						
Are the resources required small?	–	–	✓	✓✓	✓	–
Feasibility						
Is the option (or recommendation) feasible to implement?	–	–	–	✓✓✓	✓	–
Acceptability						
Is the option acceptable to key stakeholders?	–	–	✓	✓✓	✓	–
3. Expert Consensus Opinion: *BRAF* molecular testing is currently not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *BRAF* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.						
Benefits and Harms						
Are the desirable anticipated effects large?	✓	–	–	✓	–	–
Are the undesirable anticipated effects small?	–	–	–	✓	✓	–

Supplemental Table 3. Evidence-to-Decision Ratings, Continued

	No	Probably No	Uncertain	Probably Yes	Yes	Varies
Are the desirable effects large relative to undesirable effects?	–	–	–	✓	✓	–
3. Expert Consensus Opinion: *BRAF* molecular testing is currently not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *BRAF* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.						
Resources Required						
Are the resources required small?	–	✓	–	✓	–	–
Feasibility						
Is the option (or recommendation) feasible to implement?	–	–	–	✓✓	–	–
Acceptability						
Is the option acceptable to key stakeholders?	–	–	✓	–	–	✓
4. Expert Consensus Opinion: *RET* molecular testing is not recommended as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *RET* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.						
Benefits and Harms						
Are the desirable anticipated effects large?	–	✓	–	✓✓	–	–
Are the undesirable anticipated effects small?	–	–	✓	–	✓✓	–
Are the desirable effects large relative to undesirable effects?	–	–	✓	–	✓✓	–
Resources Required						
Are the resources required small?	–	✓	✓	✓	–	–
Feasibility						
Is the option (or recommendation) feasible to implement?	–	–	–	–	✓✓✓	–
Acceptability						
Is the option acceptable to key stakeholders?	–	–	–	–	✓✓✓	–
5. Expert Consensus Opinion: *ERBB2 (HER2)* molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *ERBB2 (HER2)* mutation analysis as part of a larger testing panel performed either initially or when routine *EGFR, ALK,* and *ROS1* testing is negative.						
Benefits and Harms						
Are the desirable anticipated effects large?	–	✓✓	✓	–	–	–
Are the undesirable anticipated effects small?	–	–	–	✓✓✓	–	–
Are the desirable effects large relative to undesirable effects?	–	–	–	✓✓✓	–	–

Supplemental Table 3. Evidence-to-Decision Ratings, Continued

	No	Probably No	Uncertain	Probably Yes	Yes	Varies
Resources Required						
Are the resources required small?	–	–	–	✓✓	✓	–
Feasibility						
Is the option (or recommendation) feasible to implement?	–	–	–	✓✓	✓	–
Acceptability						
Is the option acceptable to key stakeholders?	–	–	–	✓✓	✓	–
6. Expert Consensus Opinion: *KRAS* molecular testing is not indicated as a routine stand-alone assay as a sole determinant of targeted therapy. It is appropriate to include *KRAS* molecular testing as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.						
Benefits and Harms						
Are the desirable anticipated effects large?	–	✓✓✓	–	–	–	–
Are the undesirable anticipated effects small?	–	–	–	✓	✓✓	–
Are the desirable effects large relative to undesirable effects?	–	–	✓	✓	✓	–
Resources Required						
Are the resources required small?	–	–	–	✓	✓✓	–
Feasibility						
Is the option (or recommendation) feasible to implement?	–	–	–	✓	✓✓	–
Acceptability						
Is the option acceptable to key stakeholders?	–	–	–	✓	✓✓	–
7. Expert Consensus Opinion: *MET* molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *MET* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.						
Benefits and Harms						
Are the desirable anticipated effects large?	–	–	✓	–	✓	–
Are the undesirable anticipated effects small?	–	✓	–	✓	–	–
Are the desirable effects large relative to undesirable effects?	–	–	✓	✓	–	–
Resources Required						
Are the resources required small?	–	✓	✓	–	–	–

Supplemental Table 3. Evidence-to-Decision Ratings, Continued

	No	Probably No	Uncertain	Probably Yes	Yes	Varies
Feasibility						
Is the option (or recommendation) feasible to implement?	–	–	–	✓	✓	–
Acceptability						
Is the option acceptable to key stakeholders?	–	–	–	✓	–	✓
8. Recommendation: Immunohistochemistry (IHC) is an equivalent alternative to FISH for ALK testing.						
Benefits and Harms						
Are the desirable anticipated effects large?	–	–	–	✓	✓✓✓	–
Are the undesirable anticipated effects small?	✓	✓✓	–	✓	–	–
Are the desirable effects large relative to undesirable effects?	–	–	–	–	✓✓✓✓	–
Resources Required						
Are the resources required small?	–	–	–	✓✓✓✓	–	–
Feasibility						
Is the option (or recommendation) feasible to implement?	–	–	–	✓	✓✓✓	–
Acceptability						
Is the option acceptable to key stakeholders?	–	–	–	✓	✓✓✓	–
9. Expert Consensus Opinion: Multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond *EGFR*, *ALK*, and *ROS1*.						
Benefits and Harms						
Are the desirable anticipated effects large?	–	–	–	–	✓	–
Are the undesirable anticipated effects small?	–	✓	–	–	–	–
Are the desirable effects large relative to undesirable effects?	–	–	–	–	✓	–
Resources Required						
Are the resources required small?	✓	–	–	–	–	–
Feasibility						
Is the option (or recommendation) feasible to implement?	–	–	–	–	–	✓

Supplemental Table 3. Evidence-to-Decision Ratings, Continued

	No	Probably No	Uncertain	Probably Yes	Yes	Varies
Acceptability						
Is the option acceptable to key stakeholders?	–	–	–	–	–	✓
14. No Recommendation: There is currently insufficient evidence to support a recommendation for or against routine testing for ALK mutational status for lung adenocarcinoma patients with sensitizing ALK mutations who have progressed after treatment with an ALK-targeted tyrosine kinase inhibitor.						
Benefits and Harms						
Are the desirable anticipated effects large?	–	✓✓✓	✓	–	–	–
Are the undesirable anticipated effects small?	–	✓	✓	✓✓	–	–
Are the desirable effects large relative to undesirable effects?	–	–	✓✓✓✓	–	–	–
Resources Required						
Are the resources required small?	–	✓✓	✓	✓	–	–
Feasibility						
Is the option (or recommendation) feasible to implement?	–	–	✓✓	✓	–	✓
Acceptability						
Is the option acceptable to key stakeholders?	–	–	✓✓	✓	–	✓
15. No Recommendation: There is currently insufficient evidence to support the use of circulating cell-free plasma DNA (cfDNA) molecular methods for the diagnosis of primary lung adenocarcinoma.						
Benefits and Harms						
Are the desirable anticipated effects large?	–	✓	✓	–	–	–
Are the undesirable anticipated effects small?	–	–	–	✓	✓	–
Are the desirable effects large relative to undesirable effects?	–	–	–	✓✓	–	–
Resources Required						
Are the resources required small?	–	–	✓	✓	–	–
Feasibility						
Is the option (or recommendation) feasible to implement?	–	–	–	✓✓	–	–
Acceptability						
Is the option acceptable to key stakeholders?	–	–	–	✓✓	–	✓

Supplemental Table 3. Evidence-to-Decision Ratings, Continued

	No	Probably No	Uncertain	Probably Yes	Yes	Varies
16. Recommendation: In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cell-free plasma DNA (cfDNA) assay for *EGFR*.						
Benefits and Harms						
Are the desirable anticipated effects large?	–	–	–	–	✓✓	✓
Are the undesirable anticipated effects small?	–	–	–	–	✓✓	–
Are the desirable effects large relative to undesirable effects?	–	–	–	–	✓✓	–
Resources Required						
Are the resources required small?	–	–	✓	✓	–	–
Feasibility						
Is the option (or recommendation) feasible to implement?	–	–	–	✓✓	–	–
Acceptability						
Is the option acceptable to key stakeholders?	–	–	–	✓✓	–	–
17. Expert Consensus Opinion: Physicians may use cell-free plasma DNA (cfDNA) methods to identify *EGFR* T790M mutations in lung adenocarcinoma patients with progression or acquired resistance to *EGFR*-targeted tyrosine kinase inhibitors; testing of the tumor sample is recommended if the plasma result is negative.						
Benefits and Harms						
Are the desirable anticipated effects large?	–	–	–	–	✓	✓
Are the undesirable anticipated effects small?	–	–	–	–	✓✓	–
Are the desirable effects large relative to undesirable effects?	–	–	–	✓	✓	–
Resources Required						
Are the resources required small?	–	–	✓	✓	–	–
Feasibility						
Is the option (or recommendation) feasible to implement?	–	–	–	✓	✓	–
Acceptability						
Is the option acceptable to key stakeholders?	–	–	–	✓	✓	–

Supplemental Table 3. Evidence-to-Decision Ratings, Continued

	No	Probably No	Uncertain	Probably Yes	Yes	Varies
18. No Recommendation: There is currently insufficient evidence to support the use of circulating tumor cell (CTC) molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of *EGFR* or other mutations, or the identification of *EGFR* T790M mutations at the time of EGFR TKI-resistance.						
Benefits and Harms						
Are the desirable anticipated effects large?	–	✓	–	✓	–	–
Are the undesirable anticipated effects small?	–	–	–	–	✓✓	–
Are the desirable effects large relative to undesirable effects?	–	–	–	–	✓✓	–
Resources Required						
Are the resources required small?	–	–	✓	–	✓	–
Feasibility						
Is the option (or recommendation) feasible to implement?	–	–	✓	✓	–	–
Acceptability						
Is the option acceptable to key stakeholders?	–	–	✓	✓	–	–

✓ = one expert panel vote; ✓✓ = two expert panel votes; ✓✓✓ = three expert panel votes
Abbreviations: IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; TKI, tyrosine kinase inhibitor

Supplemental Table 4a. 2013 vs 2018 Grades for Strength of Recommendations

Rationale	2013 Recommendation Designation	2018 Recommendation Designation
Convincing (high) or adequate (intermediate) quality of evidence and clear benefit that outweighs any harms	Recommendation	Strong Recommendation
Adequate (intermediate) or inadequate (low) quality of evidence with balance of benefits and harms, values, or costs but panel concludes that there is sufficient evidence and/or benefit to inform a recommendation	Recommendation	Recommendation
Inadequate (low) or insufficient evidence with balance of benefits and harms, values, or costs, but panel consensus that a statement is necessary	Suggestion	Expert Consensus Opinion
Inadequate (very low) or insufficient evidence quality evidence, with balance of benefits and harms, values, or costs, but panel consensus that a statement is necessary	Expert Consensus Opinion	Expert Consensus Opinion
Insufficient evidence, confidence, or agreement of the balance of benefits and harms, values, or costs to provide a recommendation	Expert Consensus Opinion	No Recommendation

Derived from Andrews et al,[156] 2013.

Supplemental Table 4b. List of Reaffirmed Guideline Statements Rewritten Using GLIDES

Reaffirmed Guideline Statements with Updated Strength of Recommendations*	
2013 Statements	**2018 Statements**
1.1b: Recommendation: ALK molecular testing should be used to select patients for ALK-targeted tyrosine kinase inhibitor therapy, patients with lung adenocarcinoma should not be excluded from testing based on clinical characteristics.	**Strong Recommendation:** Physicians must use ALK testing to select lung adenocarcinoma patients for ALK-targeted therapy irrespective of clinical characteristics or when adenocarcinoma cannot be excluded.
2.1a: Recommendation: EGFR mutation testing should be ordered at the time of diagnosis for patients presenting with advanced stage disease (stage IV according to the 7th edition Tumor Node Metastasis (TNM) staging system) who are suitable for therapy or at time of recurrence or progression in patients who originally presented with lower stage disease but were not previously tested. **2.1b: Suggestion:** ALK rearrangement testing should be ordered at the time of diagnosis for patients presenting with advanced stage disease (stage IV according to the 7th edition TNM staging system) who are suitable for therapy or at time of recurrence or progression in patients who originally presented with lower stage disease but were not previously tested.	**Strong Recommendation:** Physicians must use EGFR and ALK molecular testing for lung adenocarcinoma patients at the time of diagnosis for patients presenting with advanced stage disease or at progression in patients who originally presented with lower stage disease but were not previously tested.
1.2: Recommendation: In the setting of lung cancer resection specimens, EGFR and ALK testing is recommended for adenocarcinomas and mixed lung cancers with an adenocarcinoma component, regardless of histologic grade. In the setting of full excised lung cancer specimens, EGFR and ALK testing is not recommended in lung cancers that lack any adenocarcinoma component, such as pure squamous cell carcinomas and pure small cell carcinomas. **1.3: Recommendation:** In the setting of more limited lung cancer specimens (biopsies, cytology) where an adenocarcinoma component cannot be completely excluded, EGFR and ALK testing may be performed in cases showing squamous or small cell histology but clinical criteria (e.g., young age, lack of smoking history) may be useful in selecting a subset of these samples for testing.	**Strong Recommendation:** Physicians may use EGFR and ALK testing in tumors with histologies other than adenocarcinoma when clinical features indicate a higher probability of an oncogenic driver.

Supplemental Table 4b. List of Reaffirmed Guideline Statements Rewritten Using GLIDES, continued

1.1a: Recommendation: EGFR molecular testing should be used to select patients for EGFR-targeted tyrosine kinase inhibitor therapy, patients with lung adenocarcinoma should not be excluded from testing based on clinical characteristics. **4.1. Expert consensus opinion:** Pathologists should use formalin-fixed, paraffin-embedded specimens or fresh, frozen, or alcohol-fixed specimens for PCR-based EGFR mutation tests. Other tissue treatments (eg, acidic or heavy metal fixatives, or decalcifying solutions) should be avoided in specimens destined for EGFR testing.	**Strong recommendation:** Physicians must use EGFR molecular testing to select lung adenocarcinoma patients for EGFR-targeted therapy, irrespective of clinical characteristics or when adenocarcinoma cannot be excluded. **Recommendation:** Pathologists should use formalin-fixed, paraffin-embedded specimens or fresh, frozen, or alcohol-fixed specimens for lung cancer biomarker molecular testing. Other tissue treatments, such as acidic or heavy metal fixatives, or acid decalcifying solutions, should be avoided in specimens destined for molecular testing.
6.4. Recommendation: Immunohistochemistry for total EGFR is not recommended for selection of EGFR TKI therapy	**Strong Recommendation:** Laboratories should not use total EGFR expression by IHC testing to select patients for EGFR-targeted tyrosine kinase inhibitor therapy.
12.1: Expert consensus opinion: EGFR mutation testing reports and ALK FISH reports should include a results and interpretation section readily understandable by clinical oncologists and by nonspecialist pathologists.	**Recommendation:** Pathologists and laboratories should ensure that lung cancer biomarker testing reports of all types include both results and interpretation sections readily understandable by clinical oncologists and by non-specialist pathologists.
13.1: Expert consensus opinion: EGFR and ALK testing validation should follow the same guidelines as for other molecular diagnostics and FISH tests.	**Strong recommendation:** Laboratories must use clinically validated lung cancer biomarker testing methods with appropriate performance characteristics, following standardized best practice guidelines for each technology.
14.1. Expert consensus opinion: Laboratories should follow similar quality control and quality assurance policies and procedures for EGFR and ALK testing in lung cancers as for other clinical laboratory assays. In particular, Laboratories performing EGFR and ALK testing for TKI therapy should enroll in proficiency testing, if available.	**Strong Recommendation:** Laboratories should ensure that lung cancer biomarker testing follows similar quality control and quality assurance policies and procedures as for other clinical laboratory assays.

Supplemental Table 4b. List of Reaffirmed Guideline Statements Rewritten Using GLIDES, continued

List of Reaffirmed Guideline Statements with No Change in the Strength of Recommendations*	
2013 Statements	**2018 Statements**
2.2a: Expert consensus opinion: EGFR testing of tumors at diagnosis from patients presenting with stage I, II, or III disease is encouraged but the decision to do so should be made locally by each laboratory, in collaboration with its oncology team. **2.2b: Expert consensus opinion:** ALK testing of tumors at diagnosis from patients presenting with stage I, II, or III disease is encouraged, but the decision to do so should be made locally by each laboratory, in collaboration with its oncology team.	**Expert Consensus Opinion:** Molecular testing of tumors at diagnosis from patients presenting with early stage disease is encouraged, but the decision to do so should be made locally by each laboratory, in collaboration with its multidisciplinary oncology team.
1.4: Recommendation: To determine EGFR and ALK status for initial treatment selection, primary tumors or metastatic lesions are equally suitable for testing.	**Recommendation:** Physicians should use molecular testing for the appropriate genetic targets on either primary or metastatic lung lesions to guide initial therapy selection.
2.3: Recommendation: Tissue should be prioritized for EGFR and ALK testing.	**Recommendation:** Pathologists and laboratories should utilize tissue sparing techniques to preserve tumor tissue for diagnosis and to enable subsequent lung cancer biomarker testing.
9.3. Expert consensus opinion: A pathologist should be involved in the selection of sections for FISH testing, by assessing tumor architecture, cytology, and specimen quality.	**Expert consensus opinion:** Pathologists should select samples for lung cancer biomarker testing.
5.3. Expert consensus opinion: A pathologist should assess the tumor content of each specimen and either perform, or guide a trained technologist to perform, microdissection for tumor cell enrichment, when needed.	**Expert consensus opinion:** Pathologists should assess the tumor content of each specimen. When indicated, pathologists should directly perform, or guide a trained technologist to perform, microdissection for tumor cell enrichment.
5.1: Expert consensus opinion: Pathologists should determine the adequacy of specimens for EGFR testing by assessing cancer cell content and DNA quantity and quality.	**Expert consensus opinion:** Pathologists should determine the adequacy of specimens for lung cancer biomarker molecular testing by assessing cancer cell content, tissue preservation, and nucleic acid quantity and quality.
1.5: Expert consensus opinion: In patients with multiple, apparently separate, primary lung adenocarcinomas, each tumor may be tested but testing of multiple different areas within a single tumor is not necessary.	**Expert consensus opinion:** In patients with multiple, apparently separate, primary lung adenocarcinomas, laboratories may test each tumor, but testing of multiple different areas within a single tumor is not necessary.

Supplemental Table 4b. List of Reaffirmed Guideline Statements Rewritten Using GLIDES, continued

3.2. Expert consensus opinion: Laboratories with average turnaround times beyond two weeks need to make available a more rapid test–either in house or through a reference laboratory–in instances of clinical urgency.	**Expert consensus opinion:** In laboratories with average turnaround times beyond two weeks, the laboratory should ensure that a more rapid in-house or reference laboratory testing option is available for specimens from patients with advanced stage lung cancer.
3.1: Expert consensus opinion: EGFR and ALK results should be available within two weeks (10 working days) of receiving the specimen in the testing laboratory.	**Expert consensus opinion:** Laboratories should have lung cancer biomarker testing results available for oncology team review within two weeks (10 working days) of receiving the specimen in the testing laboratory.
3.3. Expert consensus opinion: Laboratory departments should establish processes to ensure that specimens that have a final histopathological diagnosis are sent to outside molecular pathology laboratories within 3 working days of receiving requests and to intramural molecular pathology laboratories within 24 hours.	**Expert Consensus Opinion:** Laboratories should establish processes to ensure that specimens that have a histopathological diagnosis are sent to the molecular pathology laboratory within 3 working days of receiving requests.
9.4. Expert consensus opinion: A pathologist should participate in the interpretation of ALK FISH slides, either by performing the analysis directly or by reviewing the interpretations of cytogeneticists or technologists with specialized training in solid tumor FISH analysis.	**Expert consensus opinion:** Pathologists should participate in the interpretation of FISH, either by performing the analysis directly or by reviewing the interpretations of cytogeneticists or technologists with specialized training in solid tumor FISH analysis.
6.3 Expert consensus opinion: Clinical EGFR mutation testing should be able to detect all individual mutations that have been reported with a frequency of at least 1% of EGFR-mutated lung adenocarcinomas.	**Expert Consensus Opinion:** Clinical EGFR mutation testing should be able to detect all individual mutations that have been reported with a frequency of at least 1% of EGFR-mutated lung adenocarcinomas.
6.2. Expert consensus opinion: Laboratories should use EGFR test methods that are able to detect mutations in specimens with at least 50% cancer cell content, although laboratories are strongly encouraged to employ (or have available at an external reference laboratory) more sensitive tests that are able to detect mutations in specimens with as little as 10% cancer cells.	**Expert consensus opinion:** Laboratories should employ, or have available at an external reference laboratory, clinical lung cancer biomarker molecular testing assays that are able to detect molecular alterations in specimens with as little as 20% cancer cells.
6.5. Recommendation: EGFR copy number analysis (ie, FISH or CISH) is NOT recommended for selection of EGFR TKI therapy.	**Recommendation:** Pathologists and laboratories should not use EGFR copy number analysis (i.e., FISH or CISH) to select patients for EGFR-targeted tyrosine kinase inhibitor therapy.

Supplemental Table 4b. List of Reaffirmed Guideline Statements Rewritten Using GLIDES, continued

5.2. Expert consensus opinion: Each laboratory should establish the minimum proportion and number of cancer cells needed for mutation detection during validation.	**Expert consensus opinion:** Laboratories should establish laboratory-specific requirements for the minimum proportion and number of cancer cells needed for mutation detection during validation.

*All reaffirmed statements achieved between 94% to 98% agreement during the open comment period.

Abbreviations: CISH, chromogenic in situ hybridization; DNA, deoxyribonucleic acid; GLIDES, Guidelines Into Decision Support; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor

Supplemental Table 5. Quality Assessment Results for New Evidence Informing the 2013 Recommendations

Study	AMSTAR Assessment											Based on a SR	Funding reported	Overall Quality
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11			
Meta-Analysis (n=2)														
Wang et al[141] 2014	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	High
Chen et al[132] 2014	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Systematic Review (n=1)														
Ellison et al[133] 2013	Y	N	Y	N	N	Y	N	UC	Y	N	Y	N/A	Y	Intermediate

Study	Presence of bias as defined by ROBINs Tool				Balance between groups	Reporting of baseline characteristics	Reporting of adjustments when differences present	Funding reported	Overall Quality
	Selection	Misclassification	Attrition	Recall					
Single-arm Phase II NRCT (n=1)									
Cappuzzo et al[154] 2015	Y	N	N	N	UC	Y	Y	Y	Intermediate

Abbreviations: AMSTAR, Assessing the Methodological Quality of Systematic Reviews; N, no; N/A, not applicable; NRCT, non-randomized clinical trial; ROBINs, Risk of Bias in Non-randomized Studies of Intervention; SR, systematic review; UC, unclear; Y, yes.

Supplemental Table 6. Quality Assessment Results for Statement 1

1. Strong Recommendation: *ROS1* testing must be performed on all advanced stage lung adenocarcinoma patients, irrespective of clinical characteristics.

Study	Presence of bias as defined by ROBINs Tool				Balance between groups	Reporting of baseline characteristics	Reporting of adjustments when differences present	Funding reported	Overall Quality
	Selection	Misclassification	Attrition	Recall					
Single-arm Phase I NRCT (n=1)									
Shaw et al[45] 2014	Y	N	N	Y	NA	Y	N	Y	Intermediate
Prospective Cohort Study (n=1)									
Chen et al[88] 2014	N	N	N	N	Y	Y	N	Y	Intermediate
Prospective-Retrospective Cohort Study (n=1)									
Go et al[25] 2013	NA	NA	NA	NA	N	Y	N	Y	Intermediate - low
Retrospective Cohort Study (n=6)									
Bergethon et al[17] 2012	NA	NA	NA	NA	Y	Y	N	Y	Low
Cai et al[84] 2013	NA	NA	NA	NA	Y	Y	N	Y	Low
Warth et al[94] 2014	NA	NA	NA	NA	UC	N	N	Y	Low

Lee et al[106] 2015	NA	NA	NA	NA	Y	Y	N	Y	Low
Mazieres et al[39] 2015	NA	NA	NA	NA	Y	Y	N	Y	Low
Scheffler et al[111] 2015	NA	NA	NA	NA	N	N	N	N	Very low

Abbreviations: N, no; NA, not assessed based on study type; NRCT, non-randomized clinical trials; ROBINs, Risk of Bias in Non-randomized Studies of Intervention; UC, unclear; Y, yes.

Supplemental Table 7. Summary of Studies for Statement 1

1. Strong Recommendation: *ROS1* testing must be performed on all advanced stage lung adenocarcinoma patients, irrespective of clinical characteristics.

***ROS1* Mutational Status Association with Patient and Tumor Characteristics**			
Patient or Tumor Characteristic	**Number Studies Reporting Significant Prevalence**	**Studies**	**Number of *ROS1* rearrangements identified**
Younger age	2	Chen et al[88] 2014	12
		Bergethon et al[17] 2012	18
Adenocarcinoma	2	Go et al[25] 2013	16
		Bergethon et al[17] 2012	18
Female	2	Go et al[25] 2013	16
		Warth et al[94] 2014	68
Non-Asian (compared to Asian)	1	Bergethon et al[17] 2012	18
Never-smokers (compared to smokers)	2	Bergethon et al[17] 2012	18
		Lee et al[106] 2015	9
Advanced Disease	2	Go et al[25] 2013	16
		Bergethon et al[17] 2012	18

***ROS1* Rearrangement Positive Patients treated with Crizotinib**				
Study, Study Type	**Number of Patients treated with Crizotinib**	**Response Rate**	**Disease Control Rate**	**Overall Survival**
Shaw et al[45] 2014 NRCT	50 (25 patients with ROS1 fusion and 25 patients ROS1 rearrangement negative)	All patients: 72%; 95%CI, 58-84%	NR	NR
Mazieres et al[39] 2015 RCS	31 with ROS1 rearrangement	80%	86.6%	NR
Scheffler et al[111] 2015 RCS	5 with ROS1 rearrangement	NR	NR	Median 65.8 months (estimate as not reached); range, 44.3-87.5 months

Abbreviations: CI, confidence interval; NR, Not reported, NRCT, non-randomized controlled trial; RCS, retrospective cohort study.

Supplemental Table 8. Quality Assessment Results for Statement 2

2. Expert Consensus Opinion: ROS1 immunohistochemistry (IHC) may be used as a screening test in advanced stage lung adenocarcinoma patients; however, positive ROS1 IHC results should be confirmed by a molecular or cytogenetic method.

Study	Presence of bias as defined by ROBINs Tool				Balance between groups	Reporting of baseline characteristics	Reporting of adjustments when differences present	Funding reported	Overall Quality
	Selection	Misclassification	Attrition	Recall					
Prospective Cohort Studies (n=3)									
Mescam-Mancini et al[42] 2014	Y	N	N	N	Y	N	N	Y	Intermediate-low
Sholl et al[86] 2013	N	N	Y	N	Y	Y	N	Y	Intermediate-low
Chen et al[88] 2014	N	N	N	N	Y	Y	N	Y	Intermediate
Prospective-Retrospective Cohort Study (n=1)									
Cha et al[23] 2014	NA	NA	NA	NA	UC	N	N	Y	Low
Retrospective Cohort Studies (n=4)									
Warth et al[94] 2014	NA	NA	NA	NA	UC	N	N	Y	Low
Yoshida et al[96] 2014	NA	NA	NA	NA	Y	N	N	Y	Low
Boyle et al[99] 2015	NA	NA	NA	NA	UC	N	N	Y	Very low
Shan et al[112] 2015	NA	NA	NA	NA	Y	N	N	Y	Low

Abbreviations: N, no; NA, not assessed based on study type; ROBINs, Risk of Bias in Non-randomized Studies of Intervention; UC, unclear; Y, yes.

Supplemental Table 9. Summary of Studies for Statement 2

2. Expert Consensus Opinion: ROS1 IHC may be used as a screening test in advanced stage lung adenocarcinoma patients; however, positive ROS1 IHC results should be confirmed by a molecular or cytogenetic method.

Index Test	Reference Test	Study	Total Cases	Sensitivity of Index test	Specificity of Index Test
IHC	FISH	Mescam-Mancini et al[42] 2014	121	100%	96.9%
		Sholl et al[86] 2013	220	IHC 3+: 87.5% IHC 2-3+: 100%	IHC 3+: 98.0% IHC 2-3+: 92.0%
		Cha et al[23] 2014	330	H-score ≥ 100: 100% Extent of ≥75%: 100% Staining intensity ≥ 2+: 100%	H-score ≥ 100: 97.8% Extent of ≥75%: 96.8% Staining intensity ≥ 2+: 95.0%
		Yoshida et al[96] 2014	270	H-score ≥150 cut off: 94% ≥75% positive cells cut off: 94%	H-score ≥150 cut off: 98% ≥75% positive cells cut off: 90%

				≥2+ intensity cut off: 94%	≥2+ staining intensity cut off: 87%
		Shan et al[112] 2015	60	IHC 1+: 100% IHC 2+: 76.9%	IHC 1+: 93.6% IHC 2+: 95.7%
IHC	RT-PCR	Boyle et al[99] 2015	33	H-score cutoff of 100-130: 100%	H-score cutoff of 100-130: 100%

Abbreviations: FISH, fluorescence in situ hybridization; H-score, histo-score; IHC, immunohistochemistry; RT-PCR, reverse transcription polymerase chain reaction

Supplemental Table 10 – Quality Assessment Results for Statement 3

3. Expert Consensus Opinion: *BRAF* molecular testing is currently not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *BRAF* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.

Study	Presence of bias as defined by ROBINs Tool				Balance between groups	Reporting of baseline characteristics	Reporting of adjustments when differences present	Funding reported	Overall Quality
	Selection	Misclassification	Attrition	Recall					
Single-arm Phase II NRCT (n=2)									
Planchard et al[128] 2016	Y	N	N	N	NA	Y	N	Y	Intermediate-low
Planchard et al[129] 2016	Y	N	N	N	NA	Y	N	Y	Intermediate-low
Prospective Cohort Studies (n=4)									
Hsu et al[27] 2015	N	N	N	N	UC	Y	N	Y	Intermediate-low
Kinno et al[31] 2014	N	N	N	N	NA	N	N	Y	Low
Li et al[32] 2013	N	N	N	Y	UC	Y	N	Y	Intermediate - low
Li et al[33] 2014	N	N	N	N	UC	Y	Y	Y	Intermediate
Retrospective Cohort Studies (n=3)									
Cardarella et al[22] 2013	NA	NA	NA	NA	UC	N	N	Y	Low
Brutsugun et al[119] 2014	NA	NA	NA	NA	Y	N	N	Y	Low
Marchetti et al[36] 2011	NA	NA	NA	NA	N	N	N	Y	Very low

Abbreviations: N, no; NA, not assessed based on study type; NRCT, non-randomized controlled trial; ROBINs, Risk of Bias in Non-randomized Studies of Intervention; UC, unclear; Y, yes.

Supplemental Table 11. Summary of Studies for Statement 3

3. Expert Consensus Opinion: *BRAF* molecular testing is currently not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *BRAF* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.

***BRAF* Mutational Status Association with Patient and Tumor Characteristics**			
Patient or Tumor Characteristic	**Number Studies Reporting Significant Prevalence**	**Studies**	**Number of *BRAF* mutations identified**
Female	2	Li et al[33] 2014	26

		Marchetti et al[36] 2011	21 p.V600E mutations
Never smoker (compared with former/current smoker)	1	Marchetti et al[36] 2011	21 p.V600E mutations
Smokers (compared with non-smokers)	1	Marchetti et al[36] 2011	15 non-p.V600E mutations

***BRAF* Mutation Positive Patients treated with BRAF Inhibitor (Dabrafenib)**				
Study, Study Type	**Number of Patients treated with BRAF Inhibitor**	**Response Rate (RR)**	**Disease Control Rate**	**Progression Free Survival**
Planchard et al[128] 2016 NRCT	78 patients positive for p.V600E mutation	Partial RR: 33%; 95%CI, 23-45%	58%; 95%CI, 46-67%	NR
Planchard et a[129] 2016 NRCT	57 patients positive for p.V600E mutation Dabrafenib plus MEK inhibitor Trametinib	Overall RR: 63.2%; 95%CI, 49-75.6% (by independent reviewer)	75.4%; 95%CI, 62.2-85.9% (by independent reviewer)	8.6 months; range, 5.2-19.1 months (by independent reviewer)

Abbreviations: CI, confidence interval; NR, not reported, NRCT, non-randomized controlled trial; RR, response rate.

Supplemental Table 12. Quality Assessment Results for Statement 4

4. Expert Consensus Opinion: *RET* molecular testing is not recommended as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *RET* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.

Study	**Presence of bias as defined by ROBINs Tool**				**Balance between groups**	**Reporting of baseline characteristics**	**Reporting of adjustments when differences present**	**Funding reported**	**Overall Quality**
	Selection	**Misclassification**	**Attrition**	**Recall**					
Prospective Cohort Study (n=1)									
Wang et al[82] 2012	Y	N	N	N	Y	N	N	Y	Intermediate-low
Retrospective Cohort Studies (n=2)									
Lee et al[106] 2015	NA	NA	NA	NA	Y	Y	N	Y	Low
Tsai et al[115] 2015	NA	NA	NA	NA	Y	Y	N	Y	Low

Abbreviations: N, no; NA, not assessed based on study type; ROBINs, Risk of Bias in Non-randomized Studies of Intervention; Y, yes.

Supplemental Table 13. Summary of Studies for Statement 4

4. Expert Consensus Opinion: *RET* molecular testing is not recommended as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *RET* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.

***RET* Mutational Status Association with Patient and Tumor Characteristics**			
Patient or Tumor Characteristic	**Number Studies Reporting Significant Prevalence**	**Studies**	**Number of *RET* Rearrangements Identified**
Never smoker	1	Lee at al[106] 2015	15
Younger age (55years vs 64 years)	1	Lee at al[106] 2015	15

Clinical Outcomes of *RET* Rearrangement Positive Patients treated with Standard Care			
Study, Study Type	**Number of *RET* Rearrangement-**	**Comparison Group**	**Overall Survival**

	Positive Patients		
Tsai et al[115] 2015 RCS	17	Patients negative for *EGFR, ALK*, and *RET* alterations (n=190)	*RET*-pos: median 22.4 months; range, 8.8-36.0 months Comparator: median 12.0months; range, 9.0-15.0 *P*=.07

Abbreviations: n, number; pos, positive; RCS, retrospective cohort study.

Supplemental Table 14. Quality Assessment Results for Statement 5

5. Expert Consensus Opinion: *ERBB2 (HER2)* molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *ERBB2 (HER2)* mutation analysis as part of a larger testing panel performed either initially or when routine *EGFR, ALK,* and *ROS1* testing is negative.

Study	AMSTAR Assessment											Based on a SR	Funding reported	Overall Quality
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11			
Meta-Analysis (n=1)														
Liu et al[34] 2010	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High

Study	Presence of bias as defined by ROBINs Tool				Balance between groups	Reporting of baseline characteristics	Reporting of adjustments when differences present	Funding reported	Overall Quality
	Selection	Misclassification	Attrition	Recall					
Single-arm Phase II NRCT (n=1)									
Kris et al[126] 2015	Y	N	N	Y	NA	Y	N	Y	Intermediate
Prospective Cohort Studies (n=2)									
Hsu et al[27] 2015	N	N	N	N	UC	Y	N	Y	Intermediate-low
Yoshizaw et[97] al 2014	N	N	N	N	Y	Y	N	Y	Intermediate
Retrospective Cohort Studies (n=6)									
Aleric et al[14] 2012	NA	NA	NA	NA	Y	Y	N	N	Low
Calikusu et al[19] 2009	NA	NA	NA	NA	N	N	N	Y	Very low
Tomizawa et al[80] 2011	NA	NA	NA	NA	N	Y	N	Y	Low
Arcila et al[81] 2012	NA	NA	NA	NA	N	Y	N	Y	Low
Shan et al[113] 2015	NA	NA	NA	NA	Y	Y	N	Y	Low
Suzuki et al[114] 2015	NA	NA	NA	NA	N	N	N	Y	Very low

Abbreviations: AMSTAR, Assessing the Methodological Quality of Systematic Reviews; N, no; NA, not assessed based on study type; NRCT, non-randomized clinical trial; ROBINs, Risk of Bias in Non-randomized Studies of Intervention; SR, systematic review; UC, unclear; Y, yes.

Supplemental Table 15. Summary of Studies for Statement 5

5. Expert Consensus Opinion: *ERBB2 (HER2)* molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *ERBB2 (HER2)* mutation analysis as part of a larger testing panel performed either initially or when routine *EGFR, ALK,* and *ROS1* testing is negative.

***ERBB2(HER2)* Mutational Status Association with Patient and Tumor Characteristics**			
Patient or Tumor Characteristic	**Number Studies Reporting Significant Prevalence**	**Studies**	**Number of *ERBB2(HER2)* Alterations Identified**
Advanced stage (stage IIIB-IV vs stage I-IIIA)	1	Hsu et al[27] 2015	36 mutations
Early stage (stage I vs stage II-IV)	1	Tomizawa et al[80] 2011	13 mutations
Adenocarcinoma	2	Tomizawa et al[80] 2011	13 mutations
		Suzuki et al[114] 2015	46 mutations
Female	2	Tomizawa et al[80] 2011	13 mutations
		Suzuki et al[114]2015	222 amplifications
Never smoker	4	Tomizawa et al[80] 2011	13 mutations
		Arcila et al[81] 2012	26 mutations
		Shan et al[113] 2015	11 exon 20 insertions
		Suzuki et al[114] 2015	46 mutations
Younger age	3	Tomizawa et al[80] 2011	13 mutations
		Arcila et al[81] 2012	26 mutations
		Suzuki et al[114] 2015	222 amplifications, 46 mutations

***ERBB2* Mutation Positive and *ERBB2(HER2)* Amplification Positive Patients treated with Dacomitinib**				
Study, Study Type	**Number of Patients treated with Dacomitinib**	**Response Rate**	**Progression Free Survival**	**Overall Survival**
Kris et al[126] 2015 NRCT	26 with *ERBB2(HER2)* mutation	12.0%; 95%CI, 2.0-30.0%	Median 3 months; range, 2-4 months	Median 9.0 months; range, 7-21 months
	4 with *ERBB2(HER2)* amplification	0%; 95%CI, 0-60.0%	Median not reached	Median not reached

Abbreviations: CI, confidence interval; NRCT, non-randomized controlled trial.

Supplemental Table 16. Quality Assessment Results for Statement 6

6. Expert Consensus Opinion: *KRAS* molecular testing is not indicated as a routine stand-alone assay as a sole determinant of targeted therapy. It is appropriate to include *KRAS* molecular testing as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.

Study	**AMSTAR Assessment**											**Based on a SR**	**Funding reported**	**Overall Quality**
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	**Q11**			
Meta-Analyses (n=2)														
Mao et al[35] 2010	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	High-Intermediate
Meng et al[41] 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High

Study	Presence of bias as defined by ROBINs Tool				Balance between groups	Reporting of baseline characteristics	Reporting of adjustments when differences present	Funding reported	Overall Quality
	Selection	Misclassification	Attrition	Recall					
Prospective Cohort Studies (n=4)									
Fiala et al[24] 2013	N	N	N	N	N	N	N	Y	Low
Hsu et al[27] 2015	N	N	N	N	UC	Y	N	Y	Intermediate-low
Li et al[32] 2013	N	N	N	Y	UC	Y	N	Y	Intermediate-low
Li et al[33] 2014	N	N	N	N	UC	Y	Y	Y	Intermediate
Retrospective Cohort Study (n=1)									
Yeung et al[117] 2015	NA	NA	NA	NA	Y	Y	N	N	Low

Abbreviations: AMSTAR, Assessing the Methodological Quality of Systematic Reviews; N, no; NA, not assessed based on study type; ROBINs, Risk of Bias in Non-randomized Studies of Intervention ; SR, systematic review; UC, unclear; Y, yes.

Supplemental Table 17. Summary of Studies for Statement 6

6. Expert Consensus Opinion: *KRAS* molecular testing is not indicated as a routine stand-alone assay as a sole determinant of targeted therapy. It is appropriate to include *KRAS* molecular testing as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.

***KRAS* Mutational Status Association with Patient and Tumor Characteristics**			
Patient or Tumor Characteristic	**Number Studies Reporting Significant Prevalence**	**Studies**	**Number of *KRAS* Mutations Identified**
Current/former smoker (compared with never smoker)	5	Mao et al[35] 2010	308
		Fiala et al[24] 2013	440
		Hsu et al[27] 2015	93
		Li et al[33] 2014	429
		Yeung et al[117] 2015	17
Heavy smoker (>20 packs/year vs ≤20 packs/year)	1	Li et al[32] 2013	38
Male	2	Hsu et al[27] 2015	93
		Yeung et al[117] 2015	17
Younger age	1	Li et al[32] 2013	38
Adenocarcinoma	3	Mao et al[35] 2010	308
		Fiala et al[24] 2013	398
		Li et al[33] 2014	429
Invasive mucinous adenocarcinoma	1	Li et al[32] 2013	38

Clinical Outcomes of *KRAS* Mutations Positive Patients treated with Standard Care				
Study, Study Type	**Number of *KRAS* Mutations-Positive Patients**	**Comparison Group**	**Response Rate**	**Overall Survival**
Mao et al[35]	308	*KRAS* wild-type	*KRAS*-pos Objective RR with EGFR-TKI: 3%	NR

2010 MA		patients (n=1162)	*KRAS*-neg Objective RR with EGFR=TKI: 26%	
Meng et al[41] 2013 MA	Total not reported	*KRAS* wild-type patients	NR	HR, 1.45; 95%CI, 1.29-1.62 (HR>1 implies worse survival for KRAS pos versus KRAS wt)

Abbreviations: n, number; CI, confidence interval; HR, hazard ratio; MA, meta-analysis; neg, negative; NR, not reported, pos, positive; RR, response rate; TKI, tyrosine kinase inhibitor; wt, wild-type.

Supplemental Table 18. Quality Assessment Results for Statement 7

7. Expert Consensus Opinion: *MET* molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *MET* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.

Study	AMSTAR Assessment											Based on a SR	Funding reported	Overall Quality
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11			
Meta-Analysis (n=1)														
Guo et al[26] 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High

Study	Cochrane Risk of Bias Domains							Validated measures	Adequate F/U	ITT reported	Adequate power	Adequate power of subgroups	Conflicts reported	Overall Quality
	1	2	3	4	5	6	7							
RCTs (n=1)														
Spigel et al[47] 2013	LR	LR	UR	UR	UR	LR	Y	Y	Y	Y	Y	Y	Y	High-Intermediate

Study	Presence of bias as defined by ROBINs Tool				Balance between groups	Reporting of baseline characteristics	Reporting of adjustments when differences present	Funding reported	Overall Quality
	Selection	Misclassification	Attrition	Recall					
Prospective Cohort Study (n=1)									
Kowalczuk et al[91] 2014	N	N	N	N	Y	Y	Y	Y	Intermediate
Retrospective Cohort Studies (n=4)									
Jin et al[29] 2014	NA	NA	NA	NA	Y	N	N	Y	Low
Jurmeister et al[103] 2015	NA	NA	NA	NA	Y	Y	N	Y	Low
Noroet al[109] 2015	NA	NA	NA	NA	Y	Y	N	Y	Low
Weingertner et al[116] 2015	NA	NA	NA	NA	Y	Y	N	Y	Low

Abbreviations: AMSTAR, Assessing the Methodological Quality of Systematic Reviews; F/U, follow-up; ITT, intention to treat; LR, low risk; N, no; NA, not assessed based on study type; ROBINs, Risk of Bias in Non-randomized Studies of Intervention; RCT, randomized clinical trial; SR, systematic review; UR, unclear risk; Y, yes.

Supplemental Table 19. Summary of Studies for Statement 7

7. Expert Consensus Opinion: *MET* molecular testing is not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *MET* as part of larger testing panels performed either initially or when routine *EGFR, ALK*, and *ROS1* testing is negative.

***MET* Mutational Status Association with Patient and Tumor Characteristics**			
Patient or Tumor Characteristic	**Number Studies Reporting Significant Prevalence**	**Studies**	**Number of *MET* Mutations Identified**
Pleural invasion	1	Jurmeister et al[103] 2015	38 *MET* alterations
Lymphatic vessel invasion			
Lymph node metastases			

Clinical Outcomes of *MET* Mutation Positive Patients treated with erlotinib plus *MET* MAb				
Study, Study Type	**Number of *MET* Mutation-Positive Patients treated with *MET* MAb**	**Response Rate for *MET*-Pos**	**Progression Free Survival for *MET*-pos**	**Overall Survival for *MET*-pos**
Spigel et al[47] 2013 RCT	137 total patients randomized to *MET* MAb plus erlotinib or placebo plus erlotinib 66 patients *MET*-pos	*MET* MAb + erlotinib: 8.6% Placebo + erlotinib: 3.2%	MET MAb + erlotinib: 2.9 months Placebo + erlotinib: 1.5 months *P*=.04	MET MAb + erlotinib: 12.6 months Placebo + erlotinib: 3.8 months *P*=.002

Clinical Outcomes of *MET* Mutation Positive Patients treated with Standard Care			
Study, Study Type	**Number of *MET* Mutation-Positive Patients**	**Comparison Group**	**Overall Survival**
Guo et al[26] 2014 MA	Total not reported High *MET* gene copy number (GCN) High MET protein expression	Low *MET* GCN Low MET protein expression	Low *MET* GCN versus High *MET* GCN: HR, 1.61; 95%CI, 1.15-2.25; *P*=.005 Low MET protein expression versus High MET protein expression: HR, 2.18; 95%CI, 1.60-2.97; *P*<.001 (>1 favors poor prognosis with high ME GCN/expression)
Jin et al[29] 2014 RCS	34 with *MET* gene copy number gain (CNG)	*MET* CNG-negative	*MET* CNG-pos: median 66 months *MET* CNG-neg: median 78 months *P*=.01

Abbreviations: CI, confidence interval; CNG, copy number gain; GCN, gene copy number; HR, hazard ratio; MA, meta-analysis; MAb, monoclonal antibody; neg, negative; pos, positive; RCS, retrospective cohort study; RCT, randomized controlled trial.

Supplemental Table 20. Quality Assessment Results for Statement 8

8. Recommendation: Immunohistochemistry (IHC) is an equivalent alternative to fluorescence in situ hybridization (FISH) for ALK testing.

Study	Presence of bias as defined by ROBINs Tool				Balance between groups	Reporting of baseline characteristics	Reporting of adjustments when differences present	Funding reported	Overall Quality
	Selection	Misclassification	Attrition	Recall					
Prospective Cohort Studies (n=6)									
McLeer-Florin et al[40] 2012	Y	N	Y	N	N	N	N	N	Low
Park et al[51] 2012	Y	N	N	N	Y	Y	Y	Y	Intermediate
Minca et al[54] 2013	N	N	Y	N	Y	Y	Y	Y	Intermediate-low
To et al[55] 2013	N	N	N	Y	Y	Y	N	N	Intermediate-low
Ilie et al[102] 2015	Y	N	Y	N	Y	N	N	N	Low
Lantuejoul et al[105] 2015	Y	N	N	N	N	N	N	N	Low
Prospective-Retrospective Cohort Studies (n=3)									
Sholl et al[46] 2013	NA	NA	NA	NA	Y	Y	Y	N	Intermediate
Cutz et al[59] 2014	NA	NA	NA	NA	Y	N	N	Y	Intermediate-low
Savic et al[110] 2015	NA	NA	NA	NA	Y	N	N	N	Intermediate-low
Retrospective Cohort Studies (n=11)									
Blackhall et al[56] 2014	NA	NA	NA	NA	N	N	N	Y	Low
Conde et al[58] 2014	NA	NA	NA	NA	Y	N	N	Y	Low
Tantraworasin et al[61] 2014	NA	NA	NA	NA	Y	Y	N	Y	Low
Wang et al[62] 2014	NA	NA	NA	NA	Y	Y	N	Y	Low
Yang et al[83] 2012	NA	NA	NA	NA	Y	N	N	Y	Low
Ying et al[87] 2013	NA	NA	NA	NA	Y	Y	N	N	Low
Shan et al[93] 2014	NA	NA	NA	NA	N	N	N	N	Very low
Zwaenepoel et al[98] 2014	NA	NA	NA	NA	N	N	N	Y	Low

Gruber et al[101] 2015	NA	NA	NA	NA	Y	N	N	Y	Low
Jurmeister et al[103] 2015	NA	NA	NA	NA	Y	Y	N	Y	Low
Ali et al[118] 2014	NA	NA	NA	NA	Y	Y	N	Y	Low

Abbreviations: N, no; NA, not assessed based on study type; ROBINs, Risk of Bias in Non-randomized Studies of Intervention; Y, yes.

Supplemental Table 21. Summary of Studies for Statement 8

8. Recommendation: Immunohistochemistry (IHC) is an equivalent alternative to FISH for ALK testing.

Index Test	Reference Test	Study	Total Cases	Sensitivity of Index test	Specificity of Index Test	PPV of Index Test	NPV of Index Test
IHC	FISH	McFleer-Florin et al[40] 2012	100	95%	100%	NR	NR
		Park et al[51] 2012	262	IHC 1+ staining: 100% IHC 2-3+ staining: 80.0%	IHC 1+ staining: 97.7% IHC 2-3+ staining: 99.2%	NR	NR
		Minca et al[54] 2013	231	100%; 95%CI, 96-100%	100%; 95%CI, 97-100%	100%; 95%CI, 86-100%	100%; 95%CI, 97-100%
		To et al[55] 2013	351	100%	100%	NR	NR
		Cutz et al[59] 2014	28	Equivocal cases = positive: 100%; 95%CI, 81.5-100% Equivocal cases = negative: 100%; 95%CI, 81.5-100%	Equivocal cases = positive: 91.8%; 95%CI, 88.5-94.5% Equivocal cases = negative: 100%; 95%CI, 99.0-100%	NR	NR
		Ilie et al[102] 2015	176	81.0%	99.0%	NR	NR
		Lantuejoul et al[105] 2015	547	5A4: 87%; 95%CI, 79-92% D5F3: 92%; 95%CI, 83-97%	5A4: 89%; 95%CI, 85-92% D5F3: 76%; 95%CI, 70-82%	NR	NR
		Sholl et al[46] 2013	186	93.0%	100%	NR	NR
		Savic et al[110] 2015	303	Prospective cohort: 90.6%; 95%CI, 78.9-95.6% Retrospective cohort: 96%; 95%CI, 84.5-96%	Prospective cohort: 99.3%; 95%CI, 97.9-99.9% Retrospective cohort: 100%; 95%CI, 93.6-100%	Prospective cohort: 93.5%; 95%CI, 81.5-98.7% Retrospective cohort: 100%; 95%CI, 88-100%	Prospective cohort: 98.9%; 95%CI, 97.5-99.5% Retrospective cohort: 97.8%; 95%CI, 91.6-97.8%
		Conde et al[58] 2014	156	5A4: 98%; 95%CI, 95-100%, D5F3: 98%; 95%CI, 95-	5A4: 100%; 95%CI, 100-100% D5F3: 100%; 95%CI,	5A4: 100%; 95%CI, 100-100% D5F3: 100%; 95%CI,	5A4: 98%; 95%CI, 96-100% D5F3: 98%; 95%CI, 96-

				100%	100-100%	100-100%	100%
		Tantraworasin et al[61] 2014	267	80%; 95%CI, 75.0-84.8%	94.9%; 95%CI, 92.3-97.6%	38.1%; 95%CI, 32.3-43.9%	99.2%; 95%CI, 98.1-100%
		Wang et al[62] 2014	430	100%	98.2%	NR	NR
		Shan et al[93] 2014	297	100%	81.8%	NR	NR
		Gruber et al[101] 2015	218	D5F3: 95.0% 1A4: 100%	D5F3: 99.5% 1A4: 99.1%	NR	NR
FISH	IHC	Blackhall et al[56] 2014	1281	81.3%; 95%CI, 63.6-92.8%	99.0%; 95%CI, 96.2-99.9%	NR	NR

Abbreviations: CI, confidence interval; FISH, fluorescence in situ hybridization ; IHC, immunohistochemistry; NPV, negative predictive value; NR, not reported; PPV, positive predictive value

Supplemental Table 22. Quality Assessment Results for Statement 9

9. Expert Consensus Opinion: Multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond *EGFR, ALK,* and *ROS1*.

Study	Presence of bias as defined by ROBINs Tool				Balance between groups	Reporting of baseline characteristics	Reporting of adjustments when differences present	Funding reported	Overall Quality
	Selection	Misclassification	Attrition	Recall					
Prospective Cohort Studies (n=1)									
Tuononen et al[120] 2013	N	N	N	N	Y	N	N	Y	Intermediate-low
Prospective-Retrospective Cohort Studies (n=2)									
Han et al[152] 2014	NA	NA	NA	NA	UC	Y	N	Y	Low
Scarpa et al[153] 2013	NA	NA	NA	NA	UC	Y	N	Y	Low
Retrospective Cohort Studies (n=2)									
Drilon et al[100] 2015	NA	NA	NA	NA	UC	Y	N	Y	Low
Su et al[48] 2014	NA	NA	NA	NA	N	Y	N	N	Low

Abbreviations: N, no; NA, not assessed based on study type; ROBINs, Risk of Bias in Non-randomized Studies of Intervention; UC, unclear; Y, yes.

Supplemental Table 23. Summary of Studies for Statement 9

9. Expert Consensus Opinion: Multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond *EGFR, ALK,* and *ROS1*.

Index Test	Reference Test	Study	Concordance between Index and Reference Tests	Sensitivity of Index Test	Specificity of Index Test
IonTorrent NGS, (Thermo Fisher Waltham, MA, USA)	Sanger sequencing	Scarpa et al[153] 2013	Gene mutations identified by NGS: 24/36 Mutations confirmed by Sanger: 23/24	NR	NR
		Han et al[152] 2014	*EGFR* mutations: 90.3% *KRAS* mutation: 93.5% *PIK3CA* mutations: 90.3%	NR	NR
SNaPshot Assay (Thermo Fisher Waltham, MA, USA)		Su et al[48] 2014		100%	98.4%
NGS	Real-time PCR	Tuononen et al[120] 2013	*EGFR* mutations: 24.7% by NGS, 22.2% by PCR *KRAS* mutation: 30.8% by NGS, 32.1% by PCR	NR	NR

Abbreviation: NGS, next generation sequencing; NR, not reported, PCR, polymerase chain reaction.

Supplemental Table 24. Quality Assessment Results for Statement 12

12. Strong Recommendation: In lung adenocarcinoma patients who harbor sensitizing EGFR mutations and have progressed after treatment with an *EGFR*-targeted tyrosine kinase inhibitor, *EGFR* T790M mutational testing should be used to guide selection of treatment with third generation EGFR inhibitors.

Study	AMSTAR Assessment											Based on a SR	Funding reported	Overall Quality
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11			
Meta-Analysis (n=1)														
Ding et al[124] 2014	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	High

Study	Presence of bias as defined by ROBINs Tool				Balance between groups	Reporting of baseline characteristics	Reporting of adjustments when differences present	Funding reported	Overall Quality
	Selection	Misclassification	Attrition	Recall					
Single-arm Phase I NRCT (n=2)									
Janne et al[75] 2015	N	N	N	N	NA	Y	N	Y	Intermediate
Janjigian et al[70] 2014	Y	N	N	Y	NA	Y	N	Y	Intermediate
Prospective Cohort Study (n=1)									
Sun et al[69] 2013	Y	N	N	Y	Y	Y	N	Y	Intermediate
Retrospective Cohort Study (n=1)									
Hata et al[65]	NA	NA	NA	NA	Y	Y	N	Y	Low

2013									

Abbreviations: AMSTAR, Assessing the Methodological Quality of Systematic Reviews; N, no; NA, not assessed based on study type; NRCT, non-randomized clinical trial; ROBINs, Risk of Bias in Non-randomized Studies of Intervention; SR, systematic review; Y, yes.

Supplemental Table 25. Summary of Studies for Statement 12

12. Strong Recommendation: In lung adenocarcinoma patients who harbor sensitizing EGFR mutations and have progressed after treatment with an *EGFR*-targeted tyrosine kinase inhibitor, *EGFR* T790M mutational testing should be used to guide selection of treatment with third generation EGFR inhibitors.

Study, Study Type	Number of Patients	*EGFR* T790M Detection Timing	Post-Progression Treatment Regimen	Response Rate (RR)	Disease Control Rate	Progression Free Survival (PFS)
Ding et al[124] 2014 MA	246	Prior to first and second line TKI	NR	NR	NR	Patients with vs patients without T790M mutation prior to treatment with EGFR TKI: HR, 2.602; 95%CI, 1.011-6.695; *P*=.05
Janne et al[75] 2015 NRCT	253	NR	AZD9291	T790M-pos: 61%; 95%CI, 52-70%; n=138 T790M-neg: 21%; 95%CI, 12-34%; n=61	T790M-pos: 95%; 95%CI, 90-98%; n=138 T790M-neg: 61%; 95%CI, 47-73%; n=61	NR
Sun et al[69] 2013 PCS	70	Rebiospy post-progression	Afatinib (n=34)	T790M-pos: 5% T790M-neg: 38% *P*=.01	NR	T790M-pos: median 3.2months T790M-neg: median 4.6months *P*=.33
Janjigian et al[70] 2014 NRCT	126	Post-progression with fresh or archived tumor tissue	Afatinib plus Cetuximab	T790M-pos: 32%; 95%CI, 21.8-44.5; n=71 T790M-neg: 25%; 95%CI, 13.8-38.3; n=53 *P*=.34	NR	T790M-pos: median 4.6months T790M-neg: median 4.8months *P*=.64
Hata et al[65] 2013 RCS	78	Rebiopsy post-progression	TKI rechallenge (n=59)	NR	NR	T790M-pos: median 31.4months; range, 20.6-51.7; n=26 T790M-neg: median 11.4months; range, 10.5-17.8: n=52 *P*=.02

Abbreviations: n, number; CI, confidence interval; HR, hazard ratio; MA, meta-analysis; neg, negative; NR, not reported; NRCT, non-randomized controlled trial; PCS, prospective cohort study; pos, positive; RCS, retrospective cohort study; TKI, tyrosine kinase inhibitor.

Supplemental Table 26. Quality Assessment Results for Statement 16

16. Recommendation: In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cell-free plasma DNA (cfDNA) assay for *EGFR*.

Study	AMSTAR Assessment											Based on a SR	Funding reported	Overall Quality
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11			
Meta-Analyses (n=2)														
Luo et al[92] 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Li et al[125] 2014	Y	N	Y	N	Y	N	Y	Y	Y	N	Y	Y	Y	High-intermediate

Study	Presence of bias as defined by ROBINs Tool				Balance between groups	Reporting of baseline characteristics	Reporting of adjustments when differences present	Funding reported	Overall Quality
	Selection	Misclassification	Attrition	Recall					
Prospective Cohort Study (n=2)									
Douillard et al[90] 2014	N	N	N	N	NA	N	N	Y	Intermediate-low
Mok et al[108] 2015	N	N	N	N	Y	Y	Y	Y	High-intermediate
Prospective-Retrospective Cohort Study (n=1)									
Kukita et al[67] 2013	NA	NA	NA	NA	Y	N	N	N	Low
Oxnard et al[43] 2014	NA	NA	NA	NA	NA	N	NA	Y	Intermediate-low

Abbreviations: AMSTAR, Assessing the Methodological Quality of Systematic Reviews; N, no; NA, not assessed based on study type; ROBINs, Risk of Bias in Non-randomized Studies of Intervention; SR, systematic review; Y, yes.

Supplemental Table 27. Summary of Studies for Statement 16

16. Recommendation: In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cell-free plasma DNA (cfDNA) assay for *EGFR*.

Index Test	Reference Test	Study	Total Cases	Sensitivity of Index test	Specificity of Index Test	PPV of Index Test	NPV of Index Test	Concordance between Index and Reference Test
cfDNA from peripheral blood; multiple detection methods	Tumor tissue; multiple detection methods	Luo et al[92] 2014	2012	67.4%; 95%CI, 51.7-80.0%	93.5%; 95%CI, 88.8-96.3%	NR	NR	NR
		Li et al[125] 2014	1591	65.0%; 95%CI, 61-68%	88%; 95%CI, 86-90%	NR	NR	NR
cfDNA	Tumor	Douillard et al[90]	105 -	65.7%; 95%CI, 55.8-	99.8%; 95%CI, 99.0-	98.6%; 95%CI,	93.8%; 95%CI,	94.3%; 95%CI,

from blood; ARMS detection	tissue; ARMS detection	2014	652	74.7%; n=105	100%; n=547	92.3-100%; n=70	91.5-95.5; n=582	92.3-96.0; n=652
cfDNA from blood; PCR	Tumor tissue; PCR	Mok et al[108] 2015	447	75%	96%	94%	85%	88%
cfDNA; NGS, PNA-LNA PCR clamp	Tumor tissue; PNA-LNA PCR clamp	Kukita et al[67] 2013	54	78%; 95%CI, 44-93%	92%; 95%CI, 66-98%	NR	NR	86%; 95%CI, 66-95%
cfDNA from plasma; ddPCR	Tumor tissue; assay not reported	Oxnard et al[43] 2014†	46 (23 L858R, 23 exon 19 del)	L858R: 67%; 95%CI, 35-90% (1 copy/mL threshold) 19 del: 67%; 95%CI, 30-93% (6 copies/mL threshold)	L858R: 82%; 95%CI, 48-98% (1 copy/mL threshold) 19del: 79%; 95%CI, 49-95% (6 copies/mL threshold)	NR	NR	NR

† Sensitivity and specificity calculated from reported true positive, false positive, true negative and false negative cases for L858R and exon 19 deletion assays.
Abbreviations: ARMS, amplification refractory mutation system; cfDNA, cell-free DNA; CI, confidence interval, ddPCR, droplet digital polymerase chain reaction; n, number; NGS, next generation sequencing; NPV, negative predictive value; NR, not reported; PCR, polymerase chain reaction; PNA-LNA PCR, peptide nucleic acid-locked nucleic acid polymerase chain reaction; PPV, positive predictive value.

Supplemental Table 28. Quality Assessment Results for Statement 17

17. Expert Consensus Opinion: Physicians may use cell-free plasma DNA (cfDNA) methods to identify *EGFR* T790M mutations in lung adenocarcinoma patients with progression or acquired resistance to *EGFR*-targeted tyrosine kinase inhibitors; testing of the tumor sample is recommended if the plasma result is negative.

Study	Presence of bias as defined by ROBINs Tool				Balance between groups	Reporting of baseline characteristics	Reporting of adjustments when differences present	Funding reported	Overall Quality
	Selection	Misclassification	Attrition	Recall					
Prospective Cohort Studies (n=2)									
Wei et al[127] 2016	Y	N	N	N	N	Y	N	Y	Intermediate-low
Oxnard et al[130] 2016	Y	N	N	N	Y	N	N	Y	Intermediate-low
Retrospective Cohort Studies (n=2)									
Sakai et al[68] 2013	NA	NA	NA	NA	N	Y	N	N	Low
Wang et al[74] 2014	NA	NA	NA	NA	Y	Y	N	N	Low

Abbreviations: N, no; NA, not assessed based on study type; ROBINs, Risk of Bias in Non-randomized Studies of Intervention; Y, yes.

Supplemental Table 29. Summary of Studies for Statement 17

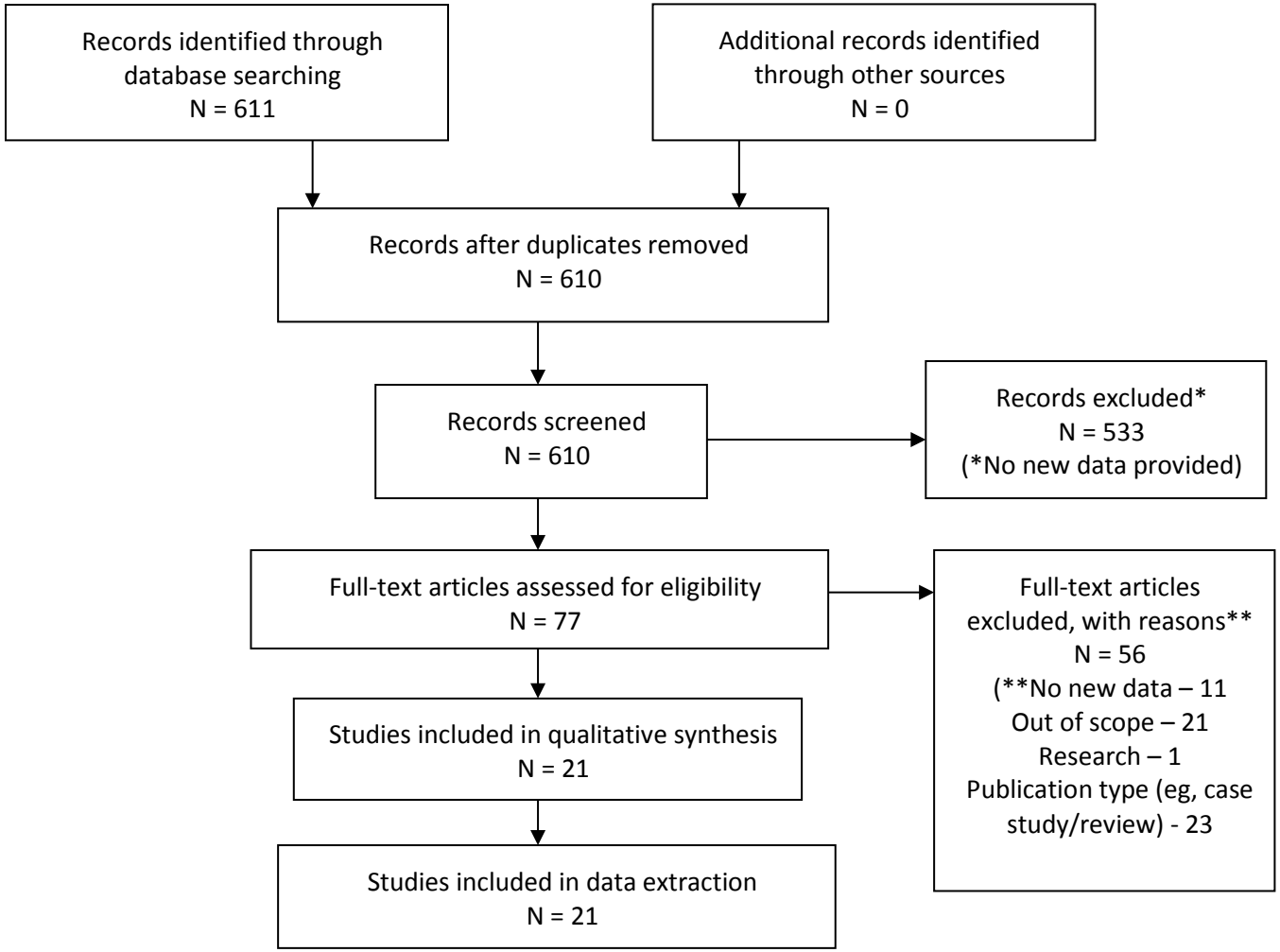
17. Expert Consensus Opinion: Physicians may use cell-free plasma DNA (cfDNA) methods to identify *EGFR* T790M mutations in lung adenocarcinoma patients with progression or acquired resistance to *EGFR*-targeted tyrosine kinase inhibitors; testing of the tumor sample is recommended if the plasma result is negative.

Study	Index Test	Reference Test	Sensitivity of Index Test	Concordance between Index and Reference Test	Objective Response Rate following treatment with 3rd-generation EGFR-TKI	Progression Free Survival following treatment with 3rd-generation EGFR-TKI
Oxnard et al[130] 2016	cfDNA from plasma; BEAMing genotyping assay (Sysmex Inostics, Mundelein, IL, USA)	Tumor tissue; BEAMing genotyping assay (Sysmex Inostics, Mundelein, IL, USA)	70.3%; 95%CI, 63-77%	NR	Tumor genotyping (n=231) T790M-pos (n=173): 62%; 95%CI, 54-70% T790M-neg (n=58): 26%; 95%CI, 15-39% *P*<.001 Plasma genotyping (n=266) T790M-pos (n=164): 63%; 95%CI, 55-70% T790M-neg (n=102): 46%; 95%CI, 36-56% *P*=.01	Tumor genotyping (n=231) T790M-pos (n=173): 9.7months; range 8.3-12.5 months T790M-neg (n=58): 3.4months; range 2.1-4.3months *P*<.001 Plasma genotyping (n=266) T790M-pos (n=164): 9.7months; range 8.3-11.1months T790M-neg (n=102): 8.2 months, range 5.3-10.9 months *P*=.19
Wei et al[127] 2016	cfDNA from peripheral blood; droplet digital PCR	Rebiopsy tissue	NR	T790M positive group: 76% T790M negative group: 88%	NR	NR
Sakai et al[68] 2013	cfDNA from plasma, peripheral blood; MassARRAY (Agena Bioscience, San Diego, CA, USA) with modification for SABER assay (Agena Bioscience, San Diego, CA, USA)	Sequencing	NR	T790M mutation detected in 21/75 plasma samples by SABER and confirmed with sequencing in 14/21 cases	NR	NR
Wang et al[74] 2014	cfDNA from peripheral blood; ARMS, digital-PCR, denaturing HPLC	Tumor tissue	NR	pre-TKI: ARMS detected T790M in 5.5% (n=6/103) and D-PCR in 31.1% (n=32/103)	NR	NR

				post-TKI: ARMS detected 25.2% (n=34/135) and D-PCR detected 43.0% (n=58/135)		

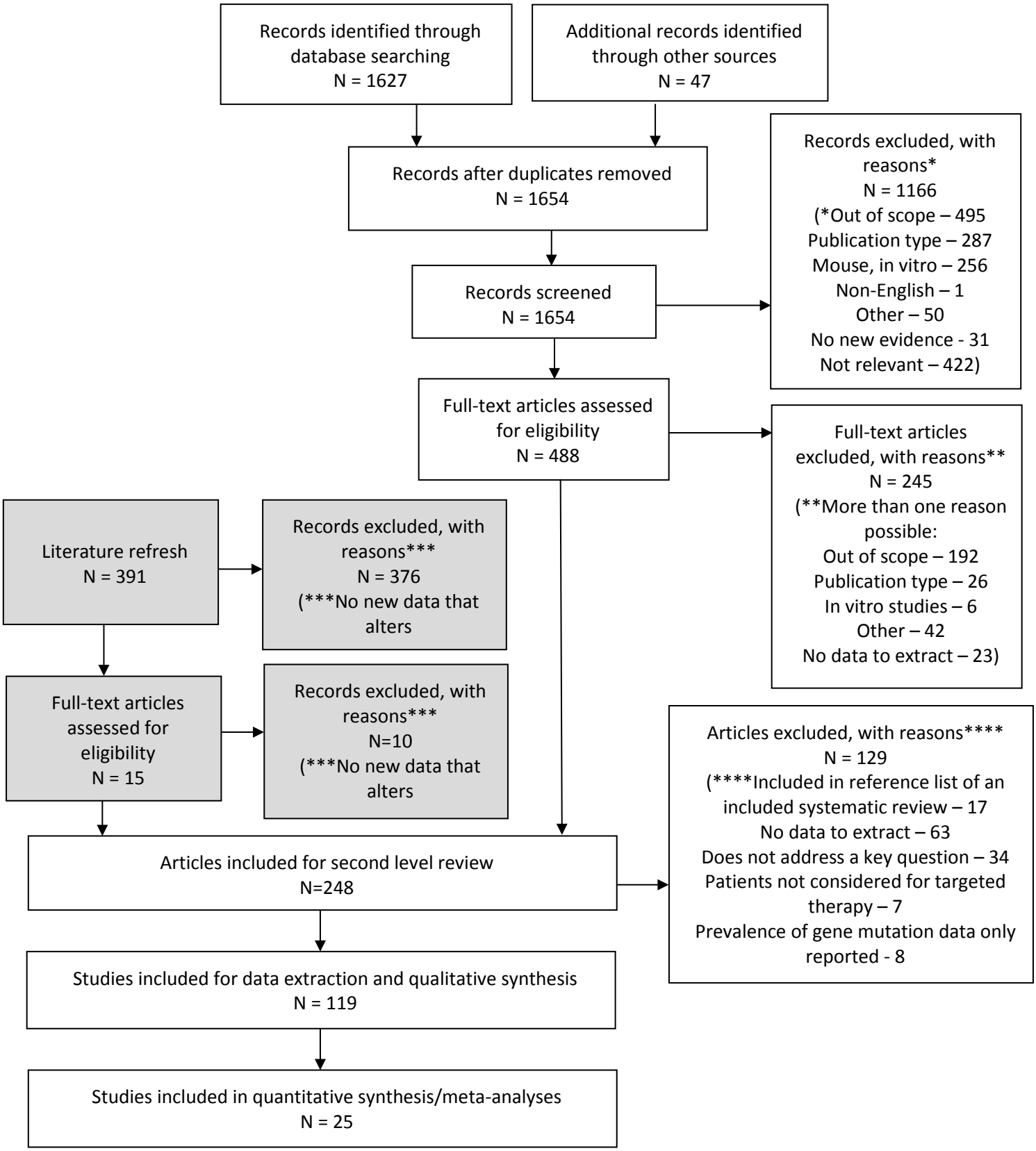
Abbreviations: ARMS, amplification refractory mutation system; cfDNA, cell free deoxyribonucleic acid; CI, confidence interval; D-PCR, digital polymerase chain reaction; HPLC, high-performance liquid chromatography; n, number; neg, negative; NR, not reported; *P*, probability value; PCR, polymerase chain reaction; pos, positive.

Supplemental Figure 1. Literature Review Flow Diagram –Reaffirmation of 2013 recommendations



*Excluded based on expert opinion, did not meet minimum quality standards, presented incomplete data or data that were not in useable formats
Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097. doi: 10.1371/journal.pmed.1000097[157]

Supplemental Figure 2. Literature Review Flow Diagram



Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097. doi: 10.1371/journal.pmed.1000097[157]

Appendix 1: Literature search strategies

Final OVID search strategy (Reaffirmation of 2013 Recommendations) – Run 5/17/15
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Ovid
MEDLINE(R) Daily Update <May 15, 2015>
Search Strategy:
---

1 *lung neoplasms/ (128612)
2 *carcinoma, non-small-cell lung/ (30288)
3 NSCLC.tw. (22334)
4 *adenocarcinoma/ (93995)
5 (lung or pulmonary).tw. (739486)
6 (cancer$ or carcinoma$ or neoplasm$ or malignan$ or tumo?r$).tw. (2350924)
7 (adenocarcinoma$ or "non?small cell").tw. (106212)
8 4 or 7 (152171)
9 5 and 8 (29696)
10 5 and 6 (212502)
11 or/1-3 (134111)
12 or/9-11 (242880)
13 (K?RAS or B?RAF or ALK? or EGFR or "epidermal growth factor receptor").tw. (57213)
14 "Kirsten ras protein".tw. (3)
15 Receptor, Epidermal Growth Factor/ (30262)
16 or/13-15 (66200)
17 (mutation or amplification or "gene copy number" or rearrangement or fusion or translocation or inversion or IHC
or immunohistochemistry or FISH or ISH or "in situ hybridization").tw. (918741)
18 12 and 16 and 17 (4513)
19 limit 18 to (english language and yr="2012 -Current") (2413)
20 animals/ not humans/ (3947090)
21 19 not 20 (2389)
22 ("cell line$" or "cell culture$" or mouse or murine or "in vitro").ti. (555059)
23 21 not 22 (2333)
24 remove duplicates from 23 (2229)
25 practice guideline/ (20132)
26 health planning guidelines/ (3885)
27 guideline*.ti. (52899)
28 (practice adj3 parameter*).ti,ab. (1241)
29 clinical protocols/ (20973)
30 guidance.ti,ab. (66887)
31 care pathway*.ti,ab. (1890)
32 critical pathway/ (4883)
33 (clinical adj3 pathway*).ti,ab. (3617)
34 algorithms/ (184927)
35 consensus development conference.pt. (9516)
36 consensus development conference nih.pt. (745)
37 or/25-36 (349019)
38 Letter/ or comment/ or editorial/ (1408794)
39 37 not 38 (334300)
40 24 and 39 (34)
41 ((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)).ti,ab. (89130)
42 (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 systhesis) or (data adj2 extract*)).ti,ab. (98980)

43 (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psychinfo not "psychinfo database") or pubmed or scopus or "sociological abstracts" or "web of science" or bids or cancerlit).ab. (96233)
44 ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. (11640)
45 evidence report: technology assessment*.jn. (220)
46 meta-analysis as topic/ (14250)
47 meta-analysis.pt. (55901)
48 (systematic adj (review$1 or overview$1)).tw. (65695)
49 (review adj5 (rationale or evidence)).ti,ab. and review.pt. (26897)
50 (exp Review Literature as Topic/ or review.pt. or exp review/) and systematic.tw. (66665)
51 ("reference list$" or bibliograph$ or hand-search$ or "relevant journals" or "manual search$").ab. (28124)
52 (pooled analy$ or "statistical pooling" or "mathematical pooling" or "statistical summar$" or "mathematical summar$" or "quantitative synthes#s" or "quantitative overview").tw. (5976)
53 ("study selection" or "selection criteria" or "data extraction" or "quality assessment" or "jadad scale" or "methodological quality").ab. (44328)
54 Review/ (1979569)
55 53 and 54 (26440)
56 or/41-52,55 (254372)
57 comment/ or letter/ or editorial/ (1408794)
58 56 not 57 (246680)
59 24 and 58 (82)
60 40 or 59 (114)
61 ("clinical trial" or "clinical trial, phase i" or "clinical trial, phase ii" or "clinical trial, phase iii" or "clinical trial, phase iv").pt. (521845)
62 "controlled clinical trial".pt. (89500)
63 "multicenter study".pt. (186681)
64 "randomized controlled trial".pt. (395487)
65 double-blind method/ (130391)
66 random allocation/ (83416)
67 single blind method/ (20469)
68 clinical trials as topic/ (172930)
69 clinical trials, phase i as topic/ (4332)
70 clinical trials, phase ii as topic/ (6174)
71 clinical trials, phase iii as topic/ (6767)
72 clinical trials, phase iv as topic/ (228)
73 exp controlled clinical trials as topic/ (103466)
74 multicenter studies as topic/ (16003)
75 (RCT or (allocat$ adj2 random$)).tw. (33154)
76 ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab. (526049)
77 early termination of clinical trials/ (357)
78 case report.tw. (219044)
79 Letter/ or comment/ or editorial/ (1408794)
80 historical article/ (316205)
81 or/78-80 (1921507)
82 or/61-77 (1283237)
83 82 not 81 (1230952)
84 24 and 83 (370)
85 24 and 82 (373)
86 remove duplicates from 85 (333)

Final OVID search strategy (New Recommendations) – Run Thursday, May 21, 2015 @ 3:27 p.m. CST.

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Ovid
MEDLINE(R) Daily Update <May 20, 2015>
Search Strategy:
---

1 *lung neoplasms/ (128711)
2 *carcinoma, non-small-cell lung/ (30315)
3 NSCLC.tw. (22335)
4 *adenocarcinoma/ (94051)
5 (lung or pulmonary).tw. (739745)
6 (cancer$ or carcinoma$ or neoplasm$ or malignan$ or tumo?r$).tw. (2352022)
7 (adenocarcinoma$ or "non?small?cell").tw. (104537)
8 4 or 7 (150553)
9 5 and 8 (28054)
10 5 and 6 (212608)
11 or/1-3 (134199)
12 or/9-11 (243010)
13 ((ROS$ or RET or MET or c?Met or B?raf or HER?2 or ERBB?2 or HGFR) adj5 (mutation$ or protein$ or activation$ or receptor$ or pathway$ or gene$ or translocation$ or rearrangement$ or oncogene$ or fusion$ or expression$ or over?expression$ or amplification$ or inversion$ or deletion$)).tw. (55143)
14 ras Proteins/ (10449)
15 Proto-oncogene proteins c-ret/ (2858)
16 proto-oncogene proteins c-met/ (3686)
17 proto-oncogene proteins b-raf/ (4455)
18 Receptor, ErbB-2/ (17223)
19 Genes, erbB-2/ (2755)
20 Ros1 protein.nm. (176)
21 MET protein, human.nm. (691)
22 or/13-21 (79074)
23 *Antibodies, Monoclonal, Humanized/ (7598)
24 *antibodies, monoclonal/ (76879)
25 exp *antineoplastic agents/ (495922)
26 exp *antineoplastic protocols/ (72676)
27 *angiogenesis inhibitors/ (12300)
28 *molecular targeted therapy/ (4610)
29 *protein kinase inhibitors/ (13643)
30 *protein-tyrosine kinases/ai (3136)
31 *receptor, epidermal growth factor/ai (3247)
32 pyrazoles/ (20078)
33 pyridines/ (43821)
34 pyrimidines/ (35905)
35 AZD9291.nm. (3)
36 BIBW 2992.nm. (153)
37 CH5424802.nm. (16)
38 CO-1686.nm. (2)
39 Bevacizumab.nm. (7314)
40 Ceritinib.nm. (21)
41 Crizotinib.nm. (381)
42 Erlotinib.nm. (2558)
43 Gefitinib.nm. (3263)
44 IMC-11F8 monoclonal antibody.nm. (9)

45 Nivolumab.nm. (91)
46 Ramucirumab.nm. (67)
47 Trastuzumab.nm. (4411)
48 (bevacizumab or ramucirumab or trastuzumab or erlotinib or afatinib or crizotinib or ceritinib or gefitinib or nivolumab or brigatinib or alectinib or necitumumab or rociletinib).tw. (21524)
49 ((tyrosine or kinase$ or egfr or c?met or met or pan?HER or HER?2 or ROS?1 or ALK? or ALK?1 or EGFR or VEGF$ or BRAF or RET$) adj3 (inhibitor$ or receptor$ or targeted)).tw. (142747)
50 (AZD?9291 or CO?1686 or IMC?11F8 or AP?26113 or CH5424802 or LDK378 or TKI$).tw. (3856)
51 ((molecular or target$) adj3 (therap$ or treatment$)).tw. (136403)
52 (Avastin or Xalkori or Tarceva or Iressa or Gilotrif or Zykadia or Cyramza or Herclon or Herceptin).tw. (3508)
53 or/23-52 (942520)
54 exp Analysis of Variance/ (287597)
55 Cluster Analysis/ (45100)
56 Decision Support Techniques/ (13458)
57 Disease Progression/ (110974)
58 Drug Resistance, Neoplasm/ (30828)
59 Prognosis/ (377858)
60 Risk Assessment/ (185547)
61 "Sensitivity and Specificity"/ (288028)
62 exp Survival Analysis/ (199631)
63 Survival Rate/ (132059)
64 exp Treatment Outcome/ (701139)
65 neoplasm recurrence, local/ (87715)
66 neoplasm metastasis/ (85048)
67 recurrence/ (151067)
68 ((improve$ or overall or time) adj3 survival).tw. (164337)
69 ((prognos$ or predict$ or therap$ or treatment) adj3 (marker$ or value or respons$)).tw. (267525)
70 (disease$ adj3 (control or surviv$)).tw. (88140)
71 ((progression$ or recurrence$ or prevalence) adj3 (disease or time or survival or rate)).tw. (173665)
72 (response and (partial or complete or rate)).tw. (285483)
73 non?respon$.tw. (15432)
74 ("clinical usefulness" or (predict$ adj3 ability)).tw. (21235)
75 RECIST.tw. (2141)
76 (statistical$ adj3 significan$).tw. (344803)
77 prognos$.ab. /freq=3 (48475)
78 ((clinicopathologic or patient$) adj3 characteristic$).tw. (56425)
79 (patient adj3 (sex or ethnicity or age or population$)).tw. (78025)
80 (smoking adj3 (history or status)).tw. (26383)
81 (hazard adj3 ratio).tw. (45197)
82 or/54-81 (3028374)
83 High-Throughput Nucleotide Sequencing/ (7194)
84 Molecular Diagnostic Techniques/ (6287)
85 Multiplex polymerase chain reaction/ (1940)
86 exp Sequence Analysis, DNA/ (168606)
87 sequence analysis, RNA/ (6790)
88 immunohistochemistry/ (254885)
89 exp Nucleic Acid Amplification Techniques/ (389333)
90 in situ hybridization, fluorescence/ (36268)
91 Sequence Analysis, Protein/ (11435)
92 Oligonucleotide Array Sequence Analysis/ (59401)
93 genome, human/ (21314)
94 exp polymerase chain reaction/ (384165)
95 nucleic acid denaturation/ (10654)

96 neoplastic cells, circulating/ (7252)
97 (circulating adj ("tumor cells" or DNA or RNA or miRNA$ or "nucleic acid")).tw. (3604)
98 (immunohistochem$ or IHC or "in situ hybridi#ation" or FISH or Sanger or PCR or antibod? or pyro?sequencing or NGS or "next?generation" or sequencing).tw. (1248110)
99 ("core biopsy" or "core needle" or "cell?block" or "fine?needle" or "paraffin?embedded" or "formalin?fixed" or FFPE or micro?dissection or micro?array).tw. (75933)
100 (detection adj3 (system? or platform$)).tw. (14318)
101 ((real?time or reverse or chain) adj3 polymerase).tw. (181299)
102 (("gene expression" or mutation?) adj3 (detection or analys#s or status or profiling)).tw. (55306)
103 (ChIP?seq$ or ChIP?array$).tw. (30)
104 (macro?dissection or micro?dissection or spectrometry or "laser capture" or fresh?frozen).tw. (174894)
105 or/83-104 (1945271)
106 "sensitivity and specificity"/ (288028)
107 "reproducibility of results"/ (291186)
108 "predictive value of tests"/ (151488)
109 Kaplan-Meier Estimate/ (35323)
110 proportional hazards models/ (49606)
111 ("laboratory method$" or "test$ method$" or "positive predictive value" or "negative predictive value" or "false positive$" or "true positive$" or "false negative$" or "true negative$" or "turn?around time").tw. (107352)
112 ((specimen or sample or diagnostic) adj3 (adequate or adequacy or sufficien$)).tw. (4551)
113 (accuracy or precision or perform$ or "limit of detection" or screen$ or confirm$ or specificity or sensitivity or algorithm or variability or heterogeneity or validat? or validity or prognostic or predictive or concordance or reproducibility).tw. (4494958)
114 or/106-113 (4755608)
115 12 and 22 and 53 and 82 (1253)
116 12 and 22 and 105 and 114 (1012)
117 115 or 116 (1808)
118 remove duplicates from 117 (1759)
119 limit 118 to (english language and yr="2007 -Current") (1329)
120 animals/ not humans/ (3948958)
121 119 not 120 (1305)
122 ("cell line$" or "cell culture$" or mouse or murine or "in vitro").ti. (555167)
123 121 not 122 (1263)
124 practice guideline/ or practice guideline.pt. (20183)
125 health planning guidelines/ (3885)
126 guideline*.ti. (52942)
127 (practice adj3 parameter*).ti,ab. (1240)
128 clinical protocols/ (20984)
129 guidance.ti,ab. (66933)
130 care pathway*.ti,ab. (1896)
131 critical pathway/ (4895)
132 (clinical adj3 pathway*).ti,ab. (3625)
133 algorithms/ (185146)
134 consensus development conference/ or consensus development conference.pt. (9521)
135 consensus development conference nih/ or consensus development conference nih.pt. (745)
136 or/124-135 (349353)
137 Letter/ or comment/ or editorial/ (1408986)
138 136 not 137 (334620)
139 ((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)).ti,ab. (89195)
140 (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 systhesis) or (data adj2 extract*)).ti,ab. (99049)

141 (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psychinfo not "psychinfo database") or pubmed or scopus or "sociological abstracts" or "web of science" or bids or cancerlit).ab. (96313)
142 ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. (11640)
143 evidence report: technology assessment*.jn. (220)
144 meta-analysis as topic/ (14256)
145 meta-analysis/ or meta-analysis.pt. (56024)
146 (systematic adj (review$1 or overview$1)).tw. (65729)
147 (review adj5 (rationale or evidence)).ti,ab. and review.pt. (26963)
148 (exp Review Literature as Topic/ or review.pt. or exp review/) and systematic.tw. (66851)
149 ("reference list$" or bibliograph$ or hand-search$ or "relevant journals" or "manual search$").ab. (28145)
150 (pooled analy$ or "statistical pooling" or "mathematical pooling" or "statistical summar$" or "mathematical summar$" or "quantitative synthes#s" or "quantitative overview").tw. (5988)
151 ("study selection" or "selection criteria" or "data extraction" or "quality assessment" or "jadad scale" or "methodological quality").ab. (44345)
152 Review/ (1981734)
153 151 and 152 (26471)
154 or/139-150,153 (254597)
155 comment/ or letter/ or editorial/ (1408986)
156 154 not 155 (246904)
157 ("clinical trial" or "clinical trial, phase i" or "clinical trial, phase ii" or "clinical trial, phase iii" or "clinical trial, phase iv").pt. (521956)
158 clinical trial/ or clinical trial, phase i/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ (521956)
159 "controlled clinical trial"/ or "controlled clinical trial".pt. (89540)
160 "multicenter study"/ or "multicenter study".pt. (186869)
161 "randomized controlled trial"/ or "randomized controlled trial".pt. (395785)
162 double-blind method/ (130450)
163 random allocation/ (83499)
164 single blind method/ (20491)
165 clinical trials as topic/ (172995)
166 clinical trials, phase i as topic/ (4332)
167 clinical trials, phase ii as topic/ (6179)
168 clinical trials, phase iii as topic/ (6773)
169 clinical trials, phase iv as topic/ (228)
170 exp controlled clinical trials as topic/ (103547)
171 multicenter studies as topic/ (16011)
172 (RCT or (allocat$ adj2 random$)).tw. (33167)
173 ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl*
or treb*) and (blind* or mask*))).ti,ab. (526303)
174 early termination of clinical trials/ (357)
175 case report.tw. (219147)
176 Letter/ or comment/ or editorial/ (1408986)
177 historical article/ (316336)
178 or/175-177 (1921921)
179 or/157-174 (1284035)
180 179 not 178 (1231721)
181 or/157-175 (1501555)
182 181 not 176 (1447444)
183 epidemiologic studies/ (6197)
184 exp case control studies/ (717372)
185 exp cohort studies/ (1437287)

186 case control.tw. (85500)
187 (cohort adj (study or studies)).tw. (101532)
188 cohort analy$.tw. (4260)
189 (follow up adj (study or studies)).tw. (39180)
190 (observational adj (study or studies)).tw. (52634)
191 cross-sectional studies/ (193993)
192 matched-pair analysis/ (4232)
193 retrospective studies/ (533224)
194 (longitudinal or retrospective or prospective or "cross sectional").tw. (967162)
195 "case series".tw. (41260)
196 case reports.pt. (1734427)
197 "case report$".tw. (259587)
198 or/183-195 (2165587)
199 or/183-197 (3857416)
200 comparative study/ or comparative study.pt. (1707965)
201 evaluation studies/ or evaluation studies.pt. (203791)
202 research support, nih, extramural/ or research support, nih, extramural.pt. (932206)
203 research support, nih, intramural/ or research support, nih, intramural.pt. (43320)
204 research support, non us gov't/ or research support, non us gov't.pt. (6152218)
205 research support, us gov't, phs/ or research support, us gov't, phs.pt. (1464417)
206 validation studies/ or validation studies.pt. or validation studies as topic/ (73837)
207 evaluation studies/ or evaluation studies.pt. or evaluation studies as topic/ (323688)
208 scientific integrity review/ or scientific integrity review.pt. (391)
209 technical report/ or technical report.pt. (2322)
210 or/200-209 (8581814)
211 comment/ or letter/ or editorial/ (1408986)
212 210 not 211 (8467709)
213 138 or 156 or 182 or 199 (5127295)
214 138 or 156 or 180 or 198 (3455194)
215 138 or 156 or 180 or 198 or 212 (10224505)
216 138 or 156 or 182 or 199 or 212 (11776223)
217 123 and 214 (443)
218 217 not 176 (442)
219 (ALK or ALK?1 or "anaplastic lymphoma kinase").tw. (5218)
220 12 and 105 and 114 and 219 (417)
221 remove duplicates from 220 (403)
222 limit 221 to (english language and yr="2012 -Current") (328)
223 222 not 120 (325)
224 223 not 122 (323)
225 224 and 214 (98)
226 225 not 176 (98)
227 drug resistance, neoplasm/ (30828)
228 ((secondary or acquired) adj3 resistance).tw. (10306)
229 227 or 228 (38761)
230 ((ROS$ or RET or MET or c?Met or B?raf or HER?2 or ERBB?2 or HGFR) adj5 (mutation$ or protein$ or activation$ or receptor$ or pathway$ or gene$ or translocation$ or rearrangement$ or oncogene$ or fusion$ or expression$ or over?expression$ amplification$ or inversion$ or deletion$)).tw. (55143)
231 ras Proteins/ (10449)
232 Proto-oncogene proteins c-ret/ (2858)
233 proto-oncogene proteins c-met/ (3686)
234 proto-oncogene proteins b-raf/ (4455)
235 Receptor, ErbB-2/ (17223)
236 Genes, erbB-2/ (2755)
237 Ros1 protein.nm. (176)

238 MET protein, human.nm. (691)
239 exp tumor markers, biological/ (189528)
240 genetic testing/ (27910)
241 genetic markers/ (47180)
242 exp gene expression/ (363838)
243 Gene Amplification/ (15202)
244 Gene Expression Profiling/ (87822)
245 Gene Expression Regulation, Neoplastic/ (77906)
246 (K?RAS or B?RAF or ALK? or EGFR or "epidermal growth factor receptor").tw. (57258)
247 "Kirsten ras protein".tw. (3)
248 Receptor, Epidermal Growth Factor/ (30288)
249 or/230-248 (836472)
250 12 and 53 and 229 and 249 (1734)
251 limit 250 to (english language and yr="2012 -Current") (885)
252 remove duplicates from 251 (812)
253 252 not 120 (803)
254 253 not 122 (747)
255 254 and 216 (566)
256 255 not 176 (563)
257 *small cell lung carcinoma/ (1585)
258 *carcinoma, squamous cell/ (79226)
259 *carcinoma, small cell/ (11644)
260 (("small cell" or "oat cell") adj5 (lung or pulmonary)).tw. (47271)
261 (lung or pulmonary).tw. or lung/ (791583)
262 258 or 259 (89975)
263 261 and 262 (16436)
264 (("squamous cancer?" or "squamous carcinoma?") adj5 (lung or pulmonary)).tw. (346)
265 257 or 260 or 263 or 264 (55785)
266 Disease Progression/ (110974)
267 Drug Resistance, Neoplasm/ (30828)
268 Prognosis/ (377858)
269 survival rate/ (132059)
270 exp Survival Analysis/ (199631)
271 exp Treatment Outcome/ (701139)
272 neoplasm recurrence, local/ (87715)
273 neoplasm metastasis/ (85048)
274 recurrence/ (151067)
275 ((improve$ or overall or time) adj3 survival).tw. (164337)
276 ((prognos$ or predict$ or therap$ or treatment) adj3 (marker$ or value or respons$)).tw. (267525)
277 (disease$ adj3 (control or surviv$)).tw. (88140)
278 ((progression$ or recurrence$ or prevalence) adj3 (disease or time or survival or rate)).tw. (173665)
279 (response adj3 (partial or complete or rate)).tw. (101318)
280 non?respon$.tw. (15432)
281 ("clinical usefulness" or (predict$ adj3 ability)).tw. (21235)
282 (hazard adj3 ratio).tw. (45197)
283 RECIST.tw. (2141)
284 (statistical$ adj3 significan$).tw. (344803)
285 prognos$.ab. /freq=3 (48475)
286 (predictive adj2 (value or marker$)).tw. (67151)
287 ((secondary or acquired) adj3 resist$).tw. (12238)
288 or/266-287 (2223123)
289 12 and 249 and 265 and 288 (7301)
290 limit 289 to (english language and yr="2011 -Current") (3366)
291 remove duplicates from 290 (3214)

292 291 not 120 (3203)
293 292 not 122 (3136)
294 ("non-small" or "non-squamous").tw. (37346)
295 293 not 294 (270)
296 295 and 214 (109)
297 296 not 176 (108)
298 (circulating adj ("tumor cells" or DNA or RNA or miRNA$ or "nucleic acid")).tw. (3604)
299 12 and 114 and 249 and 298 (128)
300 remove duplicates from 299 (121)
301 limit 300 to (english language and yr="2012 -Current") (59)
302 301 not 120 (59)
303 302 not 122 (59)
304 214 and 303 (25)
305 304 not 176 (25)
306 218 or 226 or 256 or 297 or 305

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