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Human Papillomavirus Testing in Head and Neck Cancers
Guideline from the College of American Pathologists

Corresponding Author:
James S. Lewis, Jr., MD, FCAP

Authors:
Beth Beadle, MD, PhD
Justin A. Bishop, MD, FCAP
Rebecca D. Chernock, MD, FCAP
Carol Colasacco, MLIS, SCT(ASCP)
Christina Lacchetti, MHS
Joel Todd Moncur, MD, PhD, FCAP
James W. Rocco, MD, PhD
Mary R. Schwartz, MD, FCAP
Raja R. Seethala, MD, FCAP
Nicole E. Thomas, MPH, CT(ASCP)cm
William H. Westra, MD
William C. Faquin, MD, PhD, FCAP


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METHODS USED TO PRODUCE THE GUIDELINE

Panel Composition
The College of American Pathologists (CAP) Pathology and Laboratory Quality Center (the Center) convened an expert panel (EP) consisting of pathologists, a radiation oncologist, an otolaryngologist, and a methodologist consultant to develop an evidence-based guideline to make recommendations for the testing, application, interpretation, and reporting of human papillomavirus (HPV) (and surrogate marker) tests in head and neck carcinomas in order to improve consistency and quality of clinical practice. The CAP approved the appointment of the project co-chairs and panel members. The EP members performed the systematic evidence review (SER). An advisory panel (AP) of two patient advocates, four pathologists, one medical oncologist/molecular epidemiologist, one radiation oncologist, and a methodologist 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 the CAP conflict of interest (COI) disclosure process, whose policy and form (in effect April 2010) require 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 Center uses the following criteria:

Nominees who have the following conflicts may be excused from the panel:
- a. Stock or equity interest in a commercial entity that would likely be affected by the guideline or white paper
- b. Royalties or licensing fees from products that would likely be affected by the guideline or white paper
- c. Employee of a commercial entity that would likely be affected by the guideline or white paper

Nominees who have the following potentially manageable direct conflicts may be appointed to the panel:
- a. Patents for products covered by the guideline or white paper
- b. Member of an advisory board of a commercial entity that would be affected by the guideline or white paper
- c. Payments to cover costs of clinical trials, including travel expenses associated directly with the trial
- d. Reimbursement from commercial entity for travel to scientific or educational meetings

Everyone was required to disclose conflicts prior to beginning and continuously throughout the project’s timeline. Expert panel members’ disclosed conflicts are listed in the appendix of the manuscript. The CAP 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 expert panel met 16 times through teleconference webinars from November 22, 2013 through September 21, 2016. Additional work was completed via electronic mail. The panel met in person February 8-9, 2014 to determine the scope and key questions and again April 9, 2016 to draft recommendations.
The following key questions were developed by the expert and advisory panel for which to base the literature search:

1) Should patients with newly diagnosed oropharyngeal squamous cell carcinoma (OPSCC), nonoropharyngeal SCC (non-OPSCC), oropharyngeal non-SCC, nonoropharyngeal non-SCC, and cervical nodal metastatic carcinomas of unknown and/or known primary be routinely tested for high risk (HR)-HPV?
   a. Do relevant clinical outcomes differ based on:
      i. Testing with immunohistochemistry (IHC) p16 alone?
      ii. Testing with IHC p16 plus one confirmatory test?
         1. Polymerase chain reaction (PCR) for HPV deoxyribonucleic acid (DNA)
         2. in situ hybridization (ISH) for HPV DNA
         3. ISH for E6/E7 ribonucleic acid (RNA)
         4. Reverse transcription (RT)-PCR for E6/E7
         5. Subtyping of HR-HPV
   b. Do relevant clinical outcomes differ if the diagnosis is based on fine needle aspiration (FNA) rather than biopsy?
      i. What is the comparison of testing with FNA on:
         1. IHC p16 alone?
         2. PCR alone?
         3. ISH alone?
         4. Other liquid-based tests alone?
         5. Specific combinations of tests?
      ii. Does testing FNA specimens vary based on the cytologic appearance of the metastatic head and neck SCC/non-SCC?
      iii. Do specific HR-HPV tests differ based on:
         1. The FNA sample preparation method? (eg, liquid-based cytology specimens, smears, cell block, other)
         2. The number of cells in the FNA specimen?
         3. The method of cell block preparation?
         o Thrombin
         o Cellient (Hologic, Marlborough, MA)
         o Other methods
      iv. How should HR-HPV tests on FNAs of metastatic head and neck SCC/non-SCC be validated?
         1. Is HPV status determined by FNA a reliable status of disease?
     v. Do any of these tests or testing algorithms differ based on smoking history?
       Does smoking history have an impact on the performance of HPV tests?

2) Do relevant clinical outcomes of specific tests or testing algorithms for HR-HPV differ based on:
   a. Specimen size, percent neoplastic cellularity, and cellularity (if so, what is minimum size associated with acceptable test performance?)
   b. Type and length of tissue fixation?
   c. For IHC p16 testing, specific antibodies, dilution, and testing conditions?
   d. For IHC p16, criteria/definition for a positive test?
   e. For ISH and PCR, testing conditions and criteria/definition for a “positive test”?
   f. For ISH, specific probes?
   g. What HPV type specific probes should be included?

3) For patients with OPSCC, non-OPSCC, and cervical nodal metastatic SCC, what is the optimal method of reporting HPV test results to best inform patients and clinicians about the clinical significance of the results (including considerations about uncertainty)?
   a. Do the harms and benefits of testing for HR-HPV differ based on the terminology used to report test results?
4) Should patients with recurrent/persistent OPSCC, non-OPSCC, and cervical nodal metastatic SCC be routinely tested for HR-HPV?

5) Should patients with locally and/or regionally recurrent OPSCC, non-OPSCC, and cervical nodal metastatic SCC be routinely tested for HR-HPV?

6) Should patients with distant disease be tested for HR-HPV?

All EP members participated in the SER. Each level of the SER (title-abstract, full text review, and data extraction) was performed in duplicate by two members of the EP. The co-chairs and contracted 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 displays the results of the literature review. All articles were available as discussion or background references. All members of the EP participated in developing draft recommendations, reviewing open comment feedback, finalizing and approving final recommendations, and writing/editing of the manuscript.

Peer Review
An open comment period was held from July 18, 2016 through August 8, 2016 on the CAP Web site www.cap.org. Fourteen draft recommendations, two demographic questions, and three questions about feasibility/implementability were posted for peer review. An announcement was sent to the following entities deemed to have interest:

- Advanced cell diagnostics (Newark, CA)
- Affymetrix (Santa Clara, CA)
- American Academy of Oral and Maxillofacial Pathology (AAOMP)
- American Cancer Society
- American Dental Association (ADA)
- American Head and Neck Society (AHNS)
- American Society for Clinical Pathology (ASCP)
- American Society of Clinical Oncology (ASCO)
- American Society of Cytopathology (ASC)
- American Society of Radiation Oncology (ASTRO)
- Association of Community Cancer Centers (ACCC)
- Association of Directors of Anatomic and Surgical Pathology (ADASP)
- Association of Molecular Pathology (AMP)
- Association of Pathology Chairs (APC)
- Canadian Association of Pathologists Association - Canadienne des pathologistes (CAP-ACP)
- Canadian Partnership Against Cancer (CPAC)
- Cancer Care
- Cancer Leadership Council (CLC)
- Cancer Research and Prevention Foundation (Prevent Cancer Foundation)
- Cancer Support Community
- National Comprehensive Cancer Network (NCCN)
- CAP
- Celgene (Summit, NJ)
"Agree" and "Disagree" responses were captured for every proposed recommendation. The website also received 269 written comments. 13 of the 14 draft recommendations achieved at least 80% agreement. Each expert panel member was assigned one - two draft recommendations to review and summarize participant comments. After consideration of the comments, seven draft recommendations were maintained with the original language and seven were revised. Resolution of all changes was obtained by majority consensus of the EP using nominal group technique (rounds of teleconference webinars, email discussion and multiple edited recommendations) amongst the panel members. The final recommendations were approved by the EP with a formal vote. The panel considered laboratory efficiency and feasibility throughout the entire considered judgment process.¹ Neither formal cost analysis nor cost effectiveness models were performed.

An independent review panel (IRP) was assembled to review and approve the guideline. The IRP was masked to the EP and vetted through the COI process.

**Dissemination Plans**
CAP plans to host a HPV Testing in Head and Neck resource page which will include a link to the manuscript and supplement; a summary of the recommendations, a teaching PowerPoint (Microsoft Corporation, Redmond, WA) and a frequently asked question (FAQ) document. The guideline will be promoted and presented at various society meetings.

**Systematic Evidence Review (SER)**

The objective of the SER was to identify articles that would provide data to inform recommendations for appropriate testing of the head and neck for HPV. 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 search for literature was initially performed on 3/3/14 in MEDLINE using the OvidSP interface, encompassing the publication dates of 1/1/1995 to 3/3/14. A supplemental search was performed in PubMed on 3/26/14 encompassing the publication dates of 1/1/1995 to 3/26/14. An additional search for literature published in journals not indexed in MEDLINE was performed utilizing Scopus (3/29/14) to identify relevant articles published between 1/1/1995 and 3/29/14. The literature search of the electronic databases was conducted in two arms; the first combined Medical Subject Headings (MeSH) and keywords to address the concepts “head and neck neoplasms”, “human papillomavirus (HPV)”, and “laboratory testing”, and the second combined MeSH terms and keywords for the concepts “head and neck neoplasms”, “human papillomavirus (HPV)”, and “outcomes”. The results of both arms of the search were combined and deduplicated. Limits were set for human studies published in English, and a publication filter was applied to exclude lower levels of evidence such as letters, commentaries, editorials, and case reports. The Ovid search strategy is included as Supplemental Figure 2. The PubMed and Scopus search strategies were adaptations of the Ovid search strategy.

A search for grey (unindexed) literature included a review of guideline and systematic reviews repository sites (eg, Guidelines International Network, National Guideline Clearinghouse, Cochrane Library, Prospero, Centre for Reviews and Dissemination) and relevant medical organizations’ websites to identify guidelines, protocols and standards. A review of meeting abstracts from pathology and oncology organizations from 2012-2014 (American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), College of American Pathologists (CAP), United States and Canada Academy of Pathology, European Society for Radiotherapy and Oncology, American Society for Radiation Oncology, American Society for Cytopathology, American Head and Neck Society, American Academy of Otolaryngology - Head and Neck Surgery, American Society for Clinical Pathology, International Papillomavirus Society) and expert panel recommendations completed the systematic literature review. The Ovid search was rerun on 7/11/16 to identify articles published since 3/1/2014 that provided new evidence or strength to the evidence informing the recommendations. A focused search for new guidelines, standards, or protocols and expert panel recommendations supplemented the literature refresh. Prior to submission for publication, all included meeting abstracts were checked for subsequent publication, and the data from any published studies was incorporated into the body of evidence.

**Inclusion and Exclusion Criteria**

Practice guidelines, consensus documents, systematic reviews (SRs), meta-analyses, randomized control trials (RCTs), comparative studies, reviews, case-controlled studies, case series, and evaluation studies were eligible for inclusion.

Published studies were selected for full-text review if they met each of the following criteria:

1. Patients with tissue or cytology aspiration material taken from the work-up of:
   - Oropharyngeal primaries
   - Cervical nodal metastasis of unknown primary
   - Regional or distant metastasis from known or suspected oropharyngeal primary
• Other head and neck sites (eg, sinonasal)
• All carcinomas in the head and neck (except non-epithelial origin)
• Human studies
2. Patients of all ages and gender
3. Studies published in English
4. The study compared, prospectively or retrospectively, laboratory testing methodologies or potential testing algorithms for HPV testing
5. The study addressed one of the key questions
6. The study included measureable data such as the negative predictive value (NPV) or positive predictive value (PPV) if testing methodologies used to determine HPV status, alone and in combination; negative and positive concordance across the platforms; sensitivity and specificity of individual tests and accuracy in determining HPV status.

Articles were excluded from the systematic review if they were non-comparative or qualitative studies, including editorials, commentaries, or letters; animal studies; full text articles not available in English; studies that included patients with other tumor types not specified in the inclusion criteria; studies that did not include relevant measureable data; and studies that did not address at least one of the key questions.

Outcomes of Interest
The outcomes of interest were two fold for the SER; clinical/prognostic outcomes and test characteristics. The clinical outcomes of interest included: overall survival, disease-free survival, progression-free survival, and recurrence-free survival. The SER also captured data on time to recurrence, quality of life, cost effectiveness, 3-year survival, 5-year survival, but yielded very limited data. For test characteristics the outcomes of interest included: sensitivity, specificity, reproducibility, concordance, and observer variability.

Data Extraction & Management
The data elements from an included article/document were extracted by one reviewer into standard data formats and tables developed using systematic review database software (DistillerSR, Evidence Partners Inc., Ottawa, Canada); a second reviewer confirmed accuracy and completeness. Any discrepancies in data extraction were resolved by discussion amongst the co-chairs and methodologist. A bibliographic database was established in EndNote (Thomson Reuters, Carlsbad, CA) to track all literature identified and reviewed during the study.

Quality Assessment Methods
An assessment of study quality was performed for all fully published studies meeting inclusion criteria by a research methodologist. Studies only available in abstract form did not undergo formal quality assessment. Formal quality assessment involved determining the risk of bias by assessing key indicators, based on study design and methodological rigor. These items were assessed as being either yes, no, partial, not reported (NR), or not applicable (N/A) in the following way:

Clinical practice guidelines (CPGs) were assessed for quality by confirming the following attributes were considered and incorporated in its design as recommended by the National Academy of Medicine (NAM), formerly the Institute of Medicine (IOM).²

• Based on a systematic review
• Included a multidisciplinary panel
• Patient preferences were considered
• Important patient sub-types were considered
• Methods were well-described and reproducible
• Information on potential conflicts of interest were gathered and disclosed
• Quality of the evidence was assessed
• Strength of the evidence was rated
• CPG includes a plan for updating
• Sources of funding are disclosed

Meta-analyses and systematic reviews were assessed based on A Measurement Tool to Assess Systematic Reviews (AMSTAR) tool:3
• An ‘a priori’ design provided
• Duplicate study selection and data extraction
• Comprehensive literature search performed
• Status of publication (ie, grey literature) used as an inclusion criterion
• List of studies (included and excluded) provided
• Characteristics of the included studies provided
• Scientific quality of the included studies assessed and documented
• Scientific quality of the included studies used appropriately in formulating conclusions
• Methods used to combine the findings of studies appropriate
• Likelihood of publication bias assessed
• Conflict of interest included

For studies that re-analyzed results of completed randomized control trials (RCTs), no specific instrument was used, but the following items were considered:
• Was the analysis pre-specified versus post hoc
• Differences in baseline characteristics between patients whose HPV status was assessed and those in which it was not
• Reporting of power calculations for subgroups analyses

Methodological criteria assessed for other study designs were informed by the Newcastle-Ottawa Quality Assessment Scale:4
• Study design
• Type of data collection
• Sampling method used
• Blinding of outcome assessment reported
• Sources of funding are disclosed

Each study was assessed individually, and then each study type was summarized. Finally, a summary of the overall quality of the evidence was given considering the evidence in totality.

A rating for the strength of evidence is given for guideline statements where quality was assessed (ie, only studies obtained from our SR). Ultimately, the designation (rating) of the strength of evidence is a judgment by the expert panel of their level of confidence that the evidence from the studies informing the recommendations reflects true effect. Supplemental Table 1 describes the grades for strength of evidence.

Quality Assessment Results
A total of 157 studies were included in our systematic review. This body of evidence comprised one meta-analysis, nine RCTs, 116 observational studies, and 31 studies only reported in abstract form. In the following sections, the quantity of the evidence as determined by the number of studies that met our inclusion criteria and were retained, the evidence type as determined by study design, the quality of that evidence as determined by the risk of bias assessment, and its consistency are all reported, both as individual studies and in totality, statement by statement. Refer to Supplemental Tables 2-6 for these findings.

Assessing the Strength of Recommendations
The central questions that the EP addressed in developing the guideline was:
1) Should patients should be routinely tested for HR-HPV in the head and neck and if so, which ones and by what test or tests?

2) Do clinical outcomes differ based on testing methodology or other testing characteristics?

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 or Inadequate, based on four published criteria. Strength of evidence is a key element in determining the strength of a recommendation.

3) What is the strength of each recommendation? The method for determining strength of recommendation is described in the manuscript and is based on the strength of evidence and the likelihood that further studies will change the conclusions. Another consideration is the likelihood that additional studies will be conducted to fill gaps in knowledge. Recommendations not supported by evidence (ie, evidence was missing or insufficient to permit a conclusion to be reached) were made based on consensus expert opinion.

4) What is the net balance of benefits and harms? For each guideline statement, the panel considered the desirable effects, the undesirable effects, the resources required, feasibility, and acceptability.

Discussion of Benefits and Risks of Implementing the Recommendations

Statement 1: Pathologists should perform HR-HPV testing on all patients with newly diagnosed OPSCC including all histologic subtypes. This testing may be performed on the primary tumor or on a regional lymph node metastasis when the clinical findings are consistent with an oropharyngeal primary.

Identifying the HPV status of OPSCC is important for prognostication. It is also helpful for diagnosis, staging, therapy, and prognosis. p16 is relatively inexpensive, common, easy to perform for most laboratories and easy to interpret for
most pathologists. There is low interobserver variability in its assessment. The optimal performance of HPV-specific tests will help to clarify patient HPV status in situations where p16 does not perform as well due to variable clinical contexts, tissue fragmentation, technical problems with specimens, or specific clinical/research need to clarify HPV subtype

While p16 is recommended, there are some associated risks. Sensitivity and specificity of the IHC may vary across laboratories. The current literature does not clearly allow for the recommendation of a specific antibody clone nor staining conditions. In the interim, p16 IHC testing should follow the practices used in the large studies which have validated its use, and the testing must be properly validated using CAP standards. Another risk is that pathologists may not use proper interpretive criteria. Several high quality studies have also shown that p16 is sometimes overexpressed in the absence of high risk HPV, so there may be “false positives”. However, even HPV-specific tests have performance variation, with rare false negative and false positive results.

Despite these risks, the panel contends that the benefits of implementing the recommendation outweigh the harms.

**Statement 3: Pathologists should not routinely perform HR-HPV testing on patients with nonsquamous carcinomas of the oropharynx.**

Because the literature does not suggest an etiological role of HPV in nonsquamous carcinomas at this time, the panel concluded that it would not be helpful to perform testing in this context. The statement leaves room for testing to be performed in specific clinical situations, but does not support routine testing. Treating clinicians may push back and desire testing of more tumor subtypes; however, the preponderance of data at this time does not support testing of nonsquamous cancers. Not performing unnecessary testing should lead to cost, time, and laboratory resource savings.

The resources required to implement this guideline statement would be minimal. In essence, it only requires that personnel know when not to test. Laboratories may wish to inform personnel using various communication methods (such as updating standard operating procedures [SOPs]).

Most participants of the open comment period agreed with this guideline statement.

**Statement 4: Pathologists should not routinely perform HR-HPV testing on patients with nonoropharyngeal primary tumors of the head and neck.**

The systematic review did not support the use of HR-HPV testing for patients with non-OP primary tumors of the head and neck. The desirable effects include saving money, time, and resources of the laboratory. This would also trickle down in cost savings for the patients by not incurring the costs of unnecessary testing.

Because the literature does not suggest an etiological role of HPV in nonsquamous carcinomas at this time, the panel concluded that it would not be helpful to perform testing in this context. The statement leaves room for testing to be performed at times, but does not support routine testing. While this should accommodate most physicians, there might be push-back from some. Not performing unnecessary testing should lead to cost, time, and laboratory resource savings.

The resources required to implement this guideline statement would be minimal. In essence, it only requires that personnel know when not to test.

Because the literature does not support this practice, the panel contends that the desirable effects outweigh the undesirable effects for this guideline statement. Most of the participants of the open comment period agreed with this guideline statement.
Statement 5: Pathologists should routinely perform HR-HPV testing on patients with metastatic SCC of unknown primary in a upper or mid jugular chain lymph node. An explanatory note on the significance of a positive HPV result is recommended.

Level II/III metastases are already presumed to be likely oropharyngeal without HPV testing, but HPV testing is supportive evidence and helpful to counsel patient, an, regardless, will be needed later as a prognostic marker in many cases anyway as a metastatic squamous cell carcinoma at this location has a high pretest probability of association with oropharyngeal primary. Laboratories already performing HPV testing can easily add such cases to their workload since the testing methodology would be in place. Laboratories that do not perform HPV testing would incur the costs, time, and resources required to add HPV testing to their laboratory test menu or to send tests to a reference laboratory. The panel could think of no other risks or harms associated with implementing this guideline statement.

Statement 6: For tissue specimens (ie, noncytology) from patients presenting with metastatic SCC of unknown primary in a cervical upper- or mid-jugular chain lymph node, pathologists should perform p16 IHC.

Note: Additional HR-HPV testing on p16-positive cases should be performed for tumors located outside of level II or III (nonroutine testing) in the neck and/or for tumors with keratinizing morphology.

Performing p16 IHC in this context may reduce unnecessary testing for laboratories that routinely perform p16 and HPV-specific testing.

On the other hand, rare cases may be identified as p16 positive/negative without further HPV testing that may be misclassified. The clinical significance of these cases is unknown because they are so rare

Implementing this guideline statement would probably reduce testing in many cases and would save resources; but for laboratories not routinely HPV testing unknown primary SCC, it may require a small investment of resources.

Statement 7: Pathologists should perform HR-HPV testing on head and neck FNA SCC samples from all patients with known OPSCC not previously tested for HR-HPV, with suspected OPSCC, or with metastatic SCC of unknown primary.

Note: No recommendation is made for or against any specific testing methodology for HR-HPV testing in FNA samples. If the result of HR-HPV testing on the FNA sample is negative, testing should be performed on tissue if it becomes available. If pathologists use cytology samples for p16 testing, they should validate the criteria (ie, cutoff) for a positive result.

As previously mentioned, identifying the HPV status helps establish diagnosis, staging, therapy, and prognosis. Most laboratories receiving FNAs are likely already equipped to provide HR-HPV testing on these specimens because they are already commonly done on cervical cytology specimens. If this were to be implemented however, proper validation for head and neck specimens would be required. Implementing this guideline statement leverages equipment in the laboratory and expertise of the laboratory personnel. Because no recommendation is made regarding the use of any specific testing methodology, the guideline statement allows laboratories the autonomy to select the methodology of their choice.
Statement 8: Pathologists should report p16 IHC as positive as a surrogate for HR-HPV in tissue specimens (ie, noncytology) when there is at least 70% nuclear and cytoplasmic expression with at least moderate to strong intensity.

Implementing this guideline statement would impact all p16 IHC users and provide much needed standardization for what is called “positive.” Since the 70% nuclear and cytoplasmic expression is a professional and somewhat subjective assessment, there is a risk of under- or over-calling borderline cases, as is the case with interpretation of all immunostain studies with cut-off points.

There are no special resources required to implement this guideline statement. It only requires that the individual assessing the staining knows what percentage of staining is necessary to call a case positive.

Ninety percent of respondents agreed with this guideline statement during the open comment period.

Statement 9: Pathologists should not routinely perform low-risk HPV testing on patients with head and neck carcinomas.

The literature does not support the use of routine low-risk HPV testing for patients with head and neck carcinomas. The desirable effects of not testing these patients would be saving the money, time, and resources of the laboratory. This would also trickle down to a cost savings for patients by not incurring the costs of unnecessary testing. The statement leaves room for testing to be performed, but does not support routine testing.

Statement 10: Pathologists should not repeat HPV testing on patients with locally recurrent, regionally recurrent, or persistent tumor if primary tumor HR-HPV status has already been established. If initial HR-HPV status was never assessed or results are unknown, testing is recommended. HPV testing may be performed on a case-by-case basis for diagnostic purposes if there is uncertainty regarding whether the tumor in question is a recurrence or a new primary SCC.

The panel believes that there is no benefit in repeating HPV testing on patients with locally recurrent, regionally recurrent, or persistent tumor if HPV status of the primary tumor has previously been established. Again, reducing unnecessary testing saves the laboratory and patient time and money. The guideline statement, however, allows for HPV testing in cases of uncertainty. In such cases, the HPV status might help establish diagnosis as a new primary tumor and for staging, therapy, and prognosis.

Statement 11: Pathologists should not routinely perform HR-HPV testing on patients with distant metastases if primary tumor HR-HPV status has been established. HPV testing may be performed on a case-by-case basis for diagnostic purposes if there is uncertainty regarding whether the tumor in question is a metastasis or a new primary SCC.

The panel believes that there is no benefit in repeating HPV testing on patients with distant metastases if it is clear that the tumor is metastatic oropharyngeal SCC and the HPV status of the primary tumor has previously been established. The guideline statement, however, allows for HPV testing in cases of uncertainty. In such cases, the HPV status might help establish diagnosis as a new primary tumor and for staging, therapy, and prognosis.

Statement 12: Pathologists should report primary OPSCCs that test positive for HR-HPV or its surrogate marker p16 as HPV positive and/or p16-positive.

Consistency in how HPV-positive OPSCCs are reported will help make it very clear to clinicians reading the report whether a tumor is HPV-related or not. The suggested terms in this guideline statement are consistent with the new World Health Organization (WHO) terminology. The risk in
implementing this guideline statement is that other organizations may suggest different terminology which may cause confusion.

**Statement 13: Pathologists should not provide a tumor grade or differentiation status for HPV-positive/p16-positive OPSCCs.**

Consistency in the way pathologists report these cases is optimal. Since one would normally equate a “high” tumor grade with poorer outcomes in OPSCC, as it is in other head and neck SCCs, removing this terminology from HPV-positive oropharyngeal SCC tumor reports will help to avoid this confusion. The only potential risk/harm that is anticipated is that pathologists will not be able to convey the morphology of the SCC clearly enough without using these terms in the reporting. However, the panel strongly believes that the benefit outweighs any potential harms.

**Statement 14: Pathologists should not alter HR-HPV testing strategy based on patient smoking history.**

The panel believes that there is no benefit in altering HR-HPV testing strategy based on patient smoking history because for patients who are active or former smokers prognosis is still better for HPV-positive tumors when compared with HPV-negative ones. The only potential risk of this recommendation is that some treating physicians may not understand the balance between smoking and HPV status in OPSCC. Some physicians may consider all patients with HPV-positive tumors to be similar. However, active smoking is proven to markedly decrease the favorable effects of HPV positivity in a patient’s tumor.
### Supplemental Table 1. Grades for Strength of Evidence

<table>
<thead>
<tr>
<th>Designation</th>
<th>Description</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convincing</td>
<td>High confidence that available evidence reflects true effect. Further research is very unlikely to change the confidence in the estimate of effect.</td>
<td>High/Intermediate quality evidence</td>
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<tr>
<td>Adequate</td>
<td>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.</td>
<td>Intermediate/Low quality of evidence</td>
</tr>
<tr>
<td>Inadequate</td>
<td>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.</td>
<td>Low/Insufficient evidence and expert panel uses formal consensus process to reach Recommendation</td>
</tr>
<tr>
<td>Insufficient</td>
<td>Evidence is insufficient to discern net effect. Any estimate of effect is very uncertain.</td>
<td>Insufficient evidence and expert panel uses formal consensus process to reach Recommendation</td>
</tr>
</tbody>
</table>


### Supplemental Table 2 – Quality Assessment for Statement 1

#### Systematic review and meta-analysis:

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>A priori design</th>
<th>Duplicate study selection &amp; data extraction</th>
<th>Literature search</th>
<th>Grey literature used</th>
<th>List included &amp; excluded studies</th>
<th>Characteristics of included studies provided</th>
<th>Quality assessed &amp; documented</th>
<th>Quality used appropriately for conclusion</th>
<th>Methods to combine used appropriately</th>
<th>Public attention assessed</th>
<th>Conflicts of Interest (COI)</th>
<th>AMS TAR Score</th>
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<tr>
<td>O’Rourke et al, 2012</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>No</td>
<td>Yes</td>
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<td>Yes</td>
<td>7/11</td>
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Assessed for quality by the AMSTAR tool (Bruyère Research Institute, Ottawa, Ontario Canada)

#### Randomized Control Trials (RCTs):

<table>
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<tr>
<th>Author, Year</th>
<th>Pre-specified or post hoc analysis</th>
<th>Differences in baseline characteristics between patients with known Human Papillomavirus (HPV) status and those with no HPV status testing</th>
<th>Power calculations for subgroup</th>
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<td>Ang et al, 2010 (RTOG 0129)</td>
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<td>Posner et al,2011</td>
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<td>Rischin et al,2010</td>
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<td>Yes, known HPV status patients had better PS, lower T category, higher haemoglobin, and were less likely to be current smokers</td>
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<td>Wu et al,2012</td>
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<td>Lassen et al,2013</td>
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<td>Fakhry et al,2014</td>
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**Observational Studies:**

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<td>Trosm an et al, 2015</td>
<td>Retrospective</td>
<td>Prospective NR</td>
<td>All qualifying patients</td>
<td>NR but report no COIs</td>
<td>Low-Moderate</td>
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<td>Liu et al, 2015</td>
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<td>NR but report no COIs</td>
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<td>Driessen et al, 2016</td>
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Abstracts - Did not undergo quality assessment
- Dunlap et al, 2014
- Lorch et al, 2012
- Austin et al, 2012
- Hasegawa et al, 2011
- Guihard et al, 2011
- Lorch et al, 2012
Supplemental Table 3 – Quality Assessment for Statement 2

Randomized Control Trials (RCTs):

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Pre-specified or post hoc analysis</th>
<th>Differences in baseline characteristics between patients with known Human Papillomavirus (HPV) status and those with no HPV status testing</th>
<th>Power calculations for subgroup</th>
<th>Overall Risk of bias (ROB)</th>
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<tr>
<td>Ang et al, 2010 (RTOG 0129)</td>
<td>Post hoc</td>
<td>No</td>
<td>No</td>
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<td>Gillison et al, 2012 (RTOG 9003 &amp; 0129)</td>
<td>Post hoc</td>
<td>No</td>
<td>No</td>
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<td>Rischin et al, 2010 (TROG 02.02)</td>
<td>Post hoc</td>
<td>Yes, known HPV status patients had better prognostic significance, lower T category, higher hemoglobin, and were less likely to be current smokers</td>
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<td>Lassen et al, 2013 (DAHANCA 5 &amp; 7)</td>
<td>Post hoc</td>
<td>Yes, p16-positive tumors were significantly smaller in T-size and were more likely to present with nodal spread compared to p16-negative tumors</td>
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<td>Fakhry et al, 2014 (RTOG 0129 &amp; 0522)</td>
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Observational Studies:

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<th>Author, Year</th>
<th>Study Design</th>
<th>Data Collection</th>
<th>Blinding (Yes/No)</th>
<th>Sampling (Consecutive/other)</th>
<th>Funding Source</th>
<th>Overall Risk of Bias (ROB)</th>
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<tr>
<td>Author, Year</td>
<td>Study Design</td>
<td>Data Collection</td>
<td>Blinding (Yes/No)</td>
<td>Sampling (Consecutive/other)</td>
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<td>Cooper et al, 2013</td>
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<td>NR but report no Conflicts of Interest (COIs)</td>
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<td>El-Mofty et al, 2006</td>
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<td>Author, Year</td>
<td>Study Design</td>
<td>Data Collection</td>
<td>Blinding (Yes/No)</td>
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<tr>
<td>Author, Year</td>
<td>Study Design</td>
<td>Data Collection</td>
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<td>Consecutive</td>
<td>Non-industry</td>
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<td>Author, Year</td>
<td>Study Design</td>
<td>Data Collection</td>
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<td>Hong et al, 59 2013</td>
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<td>Trosm an et al, 67 2015</td>
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<td>Prospective</td>
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<td>Baras ch et al, 83 2016</td>
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<td>Liu et al, 90 2015</td>
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<td>Prospective</td>
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<td>Bussu et al, 85 2014</td>
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Abstracts - Did not undergo quality assessment

- Dunlap et al, 93 2014
- Austin et al, 95 2012
- Guihard et al, 97 2011
- Broglie et al, 104 2012
- Ang et al, 106 2012
- Knoedler et al, 107 2011
- Smith et al, 108 2014
- Rakusic et al, 110 2012
- Brookes et al, 111 2014
- Valduga et al, 112 2012
- Broglie et al, 114 2011
- Lassen et al, 115 2012
- Maxwell et al, 116 2011
- Xu et al, 117 2013

Supplemental Table 4 – Quality Assessment for Statement 4
Randomized Control Trials (RCTs):

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<tr>
<th>Author, Year</th>
<th>Pre-specified or post hoc analysis</th>
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<th>Power calculations for subgroup</th>
<th>Overall Risk of bias (ROB)</th>
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<td>Chung et al, 117 2014 (RTOG 0129 &amp; 0234 &amp; 0522)</td>
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Observational Studies:
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<th>Author, Year</th>
<th>Study Design</th>
<th>Data Collection</th>
<th>Blinding</th>
<th>Sampling (Consecutive/other)</th>
<th>Funding Source</th>
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<td>Retrospective cohort</td>
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<td>Lewis et al, 2012</td>
<td>Cross sectional</td>
<td>Prospective</td>
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<td>Not consecutive, but reports no bias apparent</td>
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<td>Robinson et</td>
<td>Retrospective</td>
<td>Pros</td>
<td>NR</td>
<td>All qualifying patients</td>
<td>NR, but no conflicts</td>
<td>Low-Moderate</td>
</tr>
</tbody>
</table>
### Supplemental Table 5 – Quality Assessment for Statement 5

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Data Collection</th>
<th>Blinding</th>
<th>Sampling (Consecutive/other)</th>
<th>Covariates Accounted or Adjusted</th>
<th>Funding Source</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compton et al, 2011</td>
<td>Retrospective cohort</td>
<td>Prospective</td>
<td>Not Reported (NR)</td>
<td>All patients in database</td>
<td>Yes</td>
<td>None</td>
<td>Low-Moderate</td>
</tr>
<tr>
<td>Tribius et al, 2012</td>
<td>Retrospective cohort</td>
<td>Prospective</td>
<td>Yes</td>
<td>All patients in database</td>
<td>Yes</td>
<td>NR but reported no conflicts of interest</td>
<td>Low</td>
</tr>
<tr>
<td>Vent et al, 2017</td>
<td>Retrospective cohort</td>
<td>Prospective</td>
<td>NR</td>
<td>All patients in registry</td>
<td>No</td>
<td>Non-industry</td>
<td>Low-Moderate</td>
</tr>
</tbody>
</table>

Abstracts - Did not undergo quality assessment

Kirby et al, 2014

Stenmark et al, 2013
### Supplemental Table 6 – Quality Assessment for Statement 7

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Data Collection</th>
<th>Blinding</th>
<th>Sampling (Consecutive/other)</th>
<th>Funding Source</th>
<th>ROB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Begum et al, 2007</td>
<td>Retrospective cohort</td>
<td>Prospective</td>
<td>Not Reported (NR)</td>
<td>Consecutive</td>
<td>NR</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bishop et al, 2012</td>
<td>Retrospective cohort</td>
<td>Prospective</td>
<td>NR</td>
<td>Consecutive</td>
<td>Non-Industry</td>
<td>Low-Moderate</td>
</tr>
<tr>
<td>Guo et al, 2014</td>
<td>Retrospective cohort</td>
<td>Prospective</td>
<td>NR</td>
<td>NR</td>
<td>Non-Industry</td>
<td>Moderate</td>
</tr>
<tr>
<td>Lastra et al, 2013</td>
<td>Retrospective cohort</td>
<td>Prospective</td>
<td>NR</td>
<td>All patients in database</td>
<td>NR</td>
<td>Moderate</td>
</tr>
<tr>
<td>Vent et al, 2013</td>
<td>Retrospective cohort</td>
<td>Prospective</td>
<td>NR</td>
<td>NR</td>
<td>Non-Industry</td>
<td>Moderate</td>
</tr>
<tr>
<td>Jakscha et al, 2013</td>
<td>Cross sectional study</td>
<td>Prospective</td>
<td>Yes</td>
<td>All qualifying cases</td>
<td>NR</td>
<td>Low-Moderate</td>
</tr>
<tr>
<td>Jannapureddy et al, 2010</td>
<td>Retrospective cohort</td>
<td>Prospective</td>
<td>NR</td>
<td>All qualifying cases</td>
<td>NR</td>
<td>Moderate</td>
</tr>
<tr>
<td>Baldassarri et al, 2015</td>
<td>Retrospective cohort</td>
<td>Prospective</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>High</td>
</tr>
<tr>
<td>Holmes et al, 2015</td>
<td>Retrospective cohort</td>
<td>Prospective</td>
<td>NR</td>
<td>All qualifying cases</td>
<td>Non-Industry</td>
<td>Low-Moderate</td>
</tr>
<tr>
<td>Jalaly et al, 2015</td>
<td>Retrospective cohort</td>
<td>Prospective</td>
<td>Yes</td>
<td>Consecutive</td>
<td>Both industry and non-industry</td>
<td>Low-Moderate</td>
</tr>
<tr>
<td>Kerr et al, 2014</td>
<td>Retrospective cohort</td>
<td>Prospective</td>
<td>NR</td>
<td>Consecutive</td>
<td>No specific funding was disclosed but some conflicts of Interest (COIs)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

**Abstracts - Did not undergo quality assessment**

<table>
<thead>
<tr>
<th>Author, Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al, 2014</td>
</tr>
<tr>
<td>Fowler et al, 2012</td>
</tr>
<tr>
<td>Davis et al, 2014</td>
</tr>
<tr>
<td>Fatima et al, 2012</td>
</tr>
<tr>
<td>Inohara et al, 2012</td>
</tr>
</tbody>
</table>
Supplemental Figure 1. Literature Review Flow Diagram

Records identified through database searching
N = 1856

Additional records identified through other sources
N = 397

Records after duplicates removed
N = 2207

Records screened
N = 2207

Records excluded
N = 1301*

Full-text articles assessed for eligibility
N = 906

Full-text articles excluded**
N = 414

Studies assessed for data extraction
N = 492

Data extraction articles excluded***
N = 318

Studies initially included for data extraction
N = 170

Articles excluded##
N = 13

Final number of studies included for data extraction
N = 157

*Excluded based on expert opinion, did not address the project scope or key questions or meet inclusion criteria (1301)
**Excluded based on expert opinion, did not meet inclusion criteria (414)
***Excluded based on expert opinion, presented incomplete data or data that were not in useable formats (318)
##Excluded based on expert opinion, did not provide unique information or evidence to either refute or upgrade the strength of recommendations (585)
##Excluded based on duplicate data or did not report data for outcomes of interest (13)

Supplemental Figure 2: Human Papillomavirus Testing in Head and Neck Cancers Ovid Search Strings

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Ovid
MEDLINE(R) Daily Update <February 28, 2014> Search Strategy:

```
1      larynx/ (13110)
2      glottis/ (4571)
3      epiglottis/ (2073)
4      laryngeal mucosa/ (759)
5      exp mouth/ (230875)
6      exp jaw/ (83249)
7      pharynx/ (14204)
8      exp hypopharynx/ (1527)
9      exp nasopharynx/ (9031)
10     oropharynx/ (3190)
11     exp nasal mucosa/ (20687)
12     nasal cavity/ (8343)
13     exp salivary glands/ (32821)
14     exp paranasal sinuses/ (19364)
15     or/1-14 (354276)
16     exp "head and neck neoplasms"/ (235360)
17     HNSCC.ti,ab. (3657)
18     or/16-17 (235769)
19     exp "neoplasms, glandular and epithelial"/ (643550)
20     carcinoma, adenosquamous/ (1467)
21     neuroendocrine carcinoma/ (1860)
22     or/19-21 (643550)
23     (oropharynx$ or mouth or "oral cavity" or salivary or parotid or submandibular or larynx$ or hypopharynx$ or pharynx$ or nasal or sinus or sinonasal or tongue or head or neck).ti,ab. (661572)
24     (carcinoma? or malignan$ or neoplas$ or cancer? or tumo?r? or metastatic or metastas?s).ti,ab. (2179000)
25     lymph nodes/ (66561)
26     neck/ (22086)
27     25 and 26 (2244)
28     ("cervical lymph node?" or (neck and node)).ti,ab. (11544)
29     neoplasms, unknown primary/ (2745)
30     ("unknown primary?" or CUP).ti,ab. (14052)
31     or/29-30 (15601)
32     or/27-28 (12674)
33     15 or 23 (902767)
34     22 or 24 (2312553)
35     33 and 34 (148643)
36     31 and 32 (380)
37     18 or 35 or 36 (293791)
38     Papillomavirus infections/ (15099)
39     papillomaviridae/ (18891)
40     exp alphapapillomavirus/ (4286)
41     papillomavirus e7 proteins/ (1902)
42     oncogene proteins, viral/ (6352)
43     dna virus infections/ (1158)
44     (HPV or papillomavirus$).ti,ab. (32166)
45     ((E6 or E7) and (oncoprotein$ or protein$)).ti,ab. (4797)
46     or/38-45 (41061)
47     immunohistochemistry/ (241626)
```
human papillomavirus dna tests/ (88)
fixatives/ (4858)
tissue array analysis/ (4411)
tissue fixation/ (5183)
formaldehyde/ (17337)
paraffin embedding/ (5129)
gene expression regulation, viral/ (12319)
polymerase chain reaction/ (209591)
reverse transcriptase polymerase chain reaction/ (131686)
real-time polymerase chain reaction/ (18054)
repressor proteins/ (37051)
in situ hybridization/ (46443)
nucleic acid probes/ (492)
dna probes, hpv/ (1033)
blotting, southern/ (29765)
molecular diagnostic techniques/ (5143)
cyclin-dependent kinase inhibitor p16/ (5499)
tumor markers, biological/ (82274)
tumor suppressor protein p53/ (38343)
receptor, epidermal growth factor/ (27389)
transcription, genetic/ (146782)
oligonucleotide array sequence analysis/ (54752)
Genes, p16/ (1918)
exp "microarray analysis"/ (71474)
p16$.ti,ab. (11429)
(IHC or ICC or immunohistochemi$ or immunocytochemi$ or immunoenzyme$).ti,ab. (308856)
(PCR or ?ISH or RT?PCR).ti,ab. (327287)
(polymerase adj2 chain adj2 reaction).ti,ab. (164400)
(in adj2 situ adj2 hybridization).ti,ab. (77492)
(hybrid adj2 capture).ti,ab. (1230)
((HPV or papillomavirus or microarray$ or lab$ or test$) adj2 (method$ or platform$ or assay$)).ti,ab. (62877)
("molecular probe$" or immunostain$).ti,ab. (50979)
("formalin?fix$" or "paraffin?embedded" or FFPE).ti,ab. (1253)
"fixation time".ti,ab. (529)
(alcohol?fixed or air?dried) and smear?.ti,ab. (3)
(cell block or liquid?based or fine?needle or FNA).ti,ab. (7043)
(cytopathol$ or histopathol$ or "surgical patholog$" or cytolog$).ti,ab. (185545)
("Roche cobas" or Aptima or "Hybrid capture II" or "Hybrid capture 2" or Cervista or ProX?c or RNAscope).ti,ab. (1282)
or/47-85 (1517217)
predictive value of tests/ (137511)
prognosis/ (349649)
"sensitivity and specificity"/ (271240)
chi-square distribution/ (59803)
disease-free survival/ (40924)
false positive reactions/ (23883)
risk factors/ (544479)
observer variation/ (30765)
reproducibility of results/ (264771)
analysis of variance/ (191062)
cluster analysis/ (39228)
decision support techniques/ (11672)
diagnosis, differential/ (374192)
disease progression/ (98469)
exp early diagnosis/ (19288)
102 kaplan-meier estimate/ (27405)
103 multivariate analysis/ (81150)
104 predictive value of tests/ (137511)
105 risk assessment/ (168898)
106 exp survival analysis/ (177162)
107 survival rate/ (121996)
108 exp treatment outcome/ (627762)
109 quality of life/ (113308)
110 ((improve$ or overall or disease$ or time or rate$) and survival).ti,ab. (399138)
111 ((prognos$ or predict$ or therap$ or treatment) and (marker$ or value or respons$ or factor$)).ti,ab. (1553346)
112 ((progression$ or recurrence$) adj3 (rate$ or time or survival)).ti,ab. (75462)
113 (response rate or non?respon$).ti,ab. (71115)
114 (clinical usefulness or (prediction adj3 ability) or predictability).ti,ab. (16282)
115 (statistical$ adj3 significan$).ti,ab. (309566)
116 prognos$.ab. /freq=2 (98457)
117 prevalence.ab. /freq=2 (131125)
118 (*confidence interval" or concordance).ab. (200900)
119 (de?escalation or deintensification).ti,ab. (76)
120 or/87-119 (4340970)
121 37 and 46 and 86 (2306)
122 37 and 46 and 120 (1968)
123 121 or 122 (3099)
124 limit 123 to (english language and yr="1995 -Current") (2472)
125 (*"in vitro" or animal or mice or mouse).tw. (1865564)
126 "cell line".ti. (65689)
127 125 or 126 (1909516)
128 124 not 127 (2271)
129 Meta-Analysis as Topic/ (13247)
130 meta analysis.pt. (44479)
131 meta?analy$.tw. (1288)
132 (pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative syntheses or quantitative overview).tw. (4752)
133 (systematic adj (review$ or overview$)).tw. (50300)
134 or/129-133 (96823)
135 exp Review Literature as topic/ or review.pt. (1842343)
136 (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).tw. (187488)
137 (study adj selection).ab. (7899)
138 136 or 137 (188983)
139 135 and 138 (67804)
140 (clinical trial or clinical trial, phase II or controlled clinical trial).pt. (511253)
141 (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt. (365903)
142 random allocation/ or double blind method/ or single blind method/ (210273)
143 exp clinical trial/ or exp clinical trials as topic/ (939003)
144 (random$ control$ trial? or rct or phase?I or phase?II or phase?III or phase?IV or phase?1 or phase?2 or phase?3 or phase?4).tw. (81848)
145 or/140-144 (1027414)
146 ((singl$ or doubl$ or treb$ or tripl$) adj3 (blind$ or mask$ or dummy)).tw. (127848)
147 (allocated adj3 random).tw. (758)
148 (clinical adj3 trial$).tw. (218310)
149 or/146-148 (328792)
150 *practice guidelines/ (25568)
151 (practice adj3 guideline?).tw. (16612)
152 practice guideline.pt. (18653)
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REFERENCES


