Evidence Summary 22-2-5

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Best Practices for Oncologic Pathology Secondary Review: Head and Neck Cancer

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Report Date: June 26, 2014

This Evidence Summary is part of an eleven-report series. Please refer to #22-2-M for background and methodology.

#22-2-M: Methods and Overview
#22-2-1: Breast Cancer
#22-2-2: Gastrointestinal Cancers
#22-2-3: Genitourinary Cancers
#22-2-4: Gynecologic Cancers
#22-2-5: Head and Neck Cancers
#22-2-6: Hematologic Cancers
#22-2-7: Lung Cancer
#22-2-8: Cutaneous Melanoma and Other Skin Cancers
#22-2-9: Central Nervous System (CNS) Tumours
#22-2-10: Bone and Soft Tissue Cancers (Sarcoma)

* Author affiliations are given in Appendix I

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QUESTION
What types of specimens suspected to be or diagnosed as head and neck cancer should or should not have routine secondary pathology review?

INTRODUCTION
This evidence summary is part of a series of reports on secondary pathology review in cancer diagnosis. The reader should consult document #22-2-M: Methods and Overview for a more detailed background to the project, definitions, and limitations of secondary review, and methodology used. Only a brief summary of the methods is given below, along with any details specific to head and neck pathology.

METHODS
The evidence-based reports developed by the CCO Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (1). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and key details extracted by a PEBC methodologist (GF).

The body of evidence in this review is primarily comprised of comparative studies on interobserver accuracy or agreement. The systematic review is intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through CCO. All work produced by the PEBC is editorially independent from the Ministry.

Definition of Secondary Pathology Review
In this series of documents, secondary pathology review is defined as review of pathology specimens by a second pathologist that is initiated at the request of the patient or treating clinician, multidisciplinary case conference (MCC) process, quality control protocol, or as standard practice to review all cases at a cancer centre prior to treatment. Consultation or review at the request of the primary pathologist or prior to finalization of the primary pathologist’s report is NOT included in this definition.

Literature Search Strategy and Study Selection Criteria
Details of the search strategy and inclusion/exclusion criteria are provided in report #22-2-M of this series and only a brief summary is included here. In December 2009, a search for practice guidelines was conducted in the National Guideline Clearing House (USA), National Institute for Health and Clinical Excellence (NICE, UK), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN, USA), National Health and Medical Research Council (NHMRC, Australia), New Zealand Guidelines Group (NZGG), Canadian Medical Association’s CMA Infobase: Clinical Practice Guidelines, Association of Directors of Anatomic and Surgical Pathology, College of American Pathologists (CAP), and the Canadian Association of Pathologists (CAP-ACP). The SAGE Directory of Cancer Guidelines was searched in May 2012.

MEDLINE and EMBASE databases were searched from 1995 to May 7, 2013. Articles with terms related to both pathology (including cytology or histology) and diagnostic discrepancy were retrieved. For inclusion in this report, articles had to include review of the same samples by a second pathologist (excluding review at the original pathologist’s request), be related to the diagnosis of head and neck cancer or aspects of cancer such as grade or

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1 Cancer includes precancerous conditions that need to be distinguished from cancer, that may progress to cancer, or for which there is not general agreement as to whether they should be termed as cancer.
subtype, and report on diagnostic discrepancy or agreement between two (or more) pathologists.

RESULTS
For head and neck cancer, the search resulted in 57 articles, of which 33 were reproducibility studies. The 24 studies on head and neck cancer (2-25) that report the agreement or disagreement between initial and secondary review pathology are summarized in Table 1. There are an additional 10 studies that include head and neck cancer along with other cancers (26-35). While data was not extracted from the reproducibility studies, these may be of interest to some readers and address specialized areas of pathologic interpretation, especially areas where more research or standardization is necessary. The publications are therefore listed separately in Appendix II.

Studies from Literature Search (Table 1)
A. Thyroid
Two recent studies (15,16) reported 13% and 26% disagreement rates for thyroid fine needle aspiration (FNA), of which 8.1% and 5.3% were considered to affect treatment. Discrepancy rate and clinical relevance varied according to initial diagnosis. No studies address anaplastic carcinoma, medullary carcinoma, and non-epithelial cancers (lymphoma, sarcoma). Four studies reported that 8% to 33% of insufficient or non-diagnostic samples had discrepancies (3,12,16,19). Samples suspicious for neoplasm or malignancy had a very high discrepancy rate (e.g., 54% and 59%, respectively, in the study by Olson et al (19)).

One study reported a discrepancy rate of 14% (3) for papillary thyroid cancer, in contrast to the much higher 79% discrepancy rate for follicular neoplasms in the same study and 70% for follicular neoplasm by Park et al (55% change in treatment) (16).

B. Hemithyroidectomy /Total Thyroidectomy
Only one study on thyroid resection indicates clinical significance, reporting a 10% change in prognosis and therapy and a further 8% change in prognosis alone (6). Other studies reported 7% to 18% discrepancy rates between benign and malignant diagnoses (4,5,14). Wang et al (14) reported 43% discrepancy in subtype. An older study (1980-99) by Franc et al (5) reported 4% discrepancy for papillary carcinoma, 73% discrepancy for follicular carcinoma, and 8% for medullary carcinoma. Widder et al (9) reported a 25% change between benign and malignant for cases diagnosed as follicular adenoma, follicular carcinoma, or follicular variant of papillary thyroid cancer.

C. Mucosal (Mouth, Larynx, Oral Cavity, Tonsil) and Sinonasal Tract Biopsies
In patients referred to a department of otolaryngology-head and neck surgery for therapy, Westra et al (21) found a 6.6% discrepancy rate resulting in change in therapy or prognosis, of which 6% resulted in a change in treatment. Overall, there was a 2.6% disagreement between benign and malignant diagnoses, 1.8% change between low grade/innocuous and high grade/aggressive, and 2.2% disagreement in the type of high-grade neoplasm. Discrepancy rates were higher for some cancer sites (9% salivary gland, 10% sinonasal tract, 12% cervical lymph nodes, 16% facial skin, 17% craniofacial bones and soft tissue). Abbey et al (20) had six pathologists review specimens with hyperkeratosis or epithelial dysplasia and reported 42% to 64% disagreement in the degree of dysplasia, of which 6% to 15% had a two-step discrepancy (range based on results of different pathologists).
D. **Mucosal Resections**
   The literature review did not include any studies on discrepancy rates for secondary pathology review of mucosal resections.

E. **Salivary Gland - Resection**
   The literature review did not include any studies on discrepancy rates for secondary pathology review of salivary gland resections.

F. **Parathyroid**
   No studies on parathyroid cancer were included in the literature review.

**Guidelines**

The PEBC (36) and the National Institute for Clinical Excellence (NICE, UK) (37,38) guidelines recommend that care should be coordinated by a team including a pathologist with expertise in both histopathology and cytopathology. The PEBC guideline indicates that the pathologist should have completed a degree in medicine or equivalent, including the Royal College of Physicians and Surgeons of Canada (RCPSC) Certificate of Special Competence in Anatomical Pathology, and have enhanced knowledge and skill in the pathology of head and neck cancer malignancies acquired from either a formal fellowship or significant training in head and neck cancer at an expert centre.

Several guidelines recommend thyroid cancer specimens be reviewed by pathologists with special interest or expertise in thyroid cancer [diagnostic biopsies (37-39), smear or liquid-based cytology (40), cytopathology and pathology slides (41), differentiated thyroid cancer (DTC) and medullary thyroid cancer (MTC) (42)]. NCCN (41) indicates that although FNA is a very sensitive test, particularly for papillary thyroid cancer, false-negative results are sometimes obtained; therefore, a reassuring FNA should not override concerns in the presence of worrisome clinical findings. Molecular diagnostics to detect individual mutations in BRAF, RET, or RAS or pattern recognition approaches using molecular classifiers might be useful in the evaluation of FNA samples that are indeterminate (e.g., “follicular lesion of undetermined significance”).

The British Association of Otorhinolaryngology (42) recommends expert histopathology review of sinonasal inverted papilloma (IP). Ultrasound-guided FNAC should be used for all salivary tumours and the cytology reported by an experienced expert histopathologist.

The Canadian Ophthalmological Society (43) recommends that retinoblastoma (Rb) be diagnosed and treated in specialized centres as the disease is rare and care is complex. An ocular pathologist with retinoblastoma specialization should evaluate the optic nerve, sclera, choroid, and anterior segment for evidence of risk of tumour spread outside the eye and review the enucleated eye for high-risk features, including invasion of the optic nerve, sclera, choroid or anterior segment that could predispose to extraocular disease or metastasis.
Table 1. Pathologic discrepancy rates between primary and secondary review pathologists: Head and neck cancers.  
(Note: For ease of reading please print this table or enlarge (zoom) it to 120% on the computer monitor.)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># 2nd Reviewers</th>
<th># Specimens</th>
<th>Reviewer (Profession/Training)</th>
<th>Type of Review, Notes</th>
<th>Sample Description, Notes</th>
<th>Sample Subtype, Change or Item Compared</th>
<th># Specimens of Subtype</th>
<th>Discrepancy, %</th>
<th>Agreement %</th>
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<tbody>
<tr>
<td>Olson [19]</td>
<td>2013</td>
<td>2</td>
<td>3885</td>
<td>cytopathologist + cytopathologist</td>
<td>Institutional consultation, comparison of Bethesda System for Reporting Thyroid Cytopathology (BSRTC) classification;</td>
<td>All thyroid FNA biopsies; excluded cases sent without outside diagnosis if BSRTC category could not be determined Major=2 step change, Minor=1 step change in classification; AUS=atypia of undetermined significance; SFN=suspicious for follicular or Hurthle cell neoplasm; SFM=suspicious for malignancy</td>
<td>Overall</td>
<td>3885</td>
<td>32</td>
<td>7.7</td>
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<td>Major=change in treatment</td>
<td>272</td>
<td>19</td>
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<td>Minor=change in treatment</td>
<td>1698</td>
<td>16</td>
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<td>Surgical follow-up in 28 cases of 2-step discrepancy and found the 2nd opinion was correct in 89% of these and original pathology correct in 11%</td>
<td>779</td>
<td>61</td>
<td>12</td>
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<td>For 1-step discrepancy, follow-up indicated 44% 2nd opinion and 23% original pathology correct</td>
<td>443</td>
<td>54</td>
<td>26</td>
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<td>431</td>
<td>13</td>
<td>2.6</td>
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<td>Park [16]</td>
<td>2012</td>
<td>1</td>
<td>992</td>
<td>pathologist</td>
<td>Review of slides from all thyroid FNAC cases referred to institution 2 step disagreement or 1 step disagreement on NCI/Bethesda diagnostic terminology scale of &quot;nondiagnostic, benign, atypia of undetermined significance (AUS), suspicious for neoplasm, suspicious for malignancy, malignant&quot;</td>
<td>Thyroid FNAC Major=clinical impact (change in management, medical vs. surgical or in type of surgery) determined by pathologic and clinical follow-up via review of medical records</td>
<td>All disagreements</td>
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<td>13</td>
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<td>2 step</td>
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<td>1 step</td>
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<td>Surgical follow-up in 28 cases of 2-step discrepancy and found the 2nd opinion was correct in 89% of these and original pathology correct in 11%</td>
<td>1499</td>
<td>26</td>
<td>5.3</td>
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<td>For 1-step discrepancy, follow-up indicated 44% 2nd opinion and 23% original pathology correct</td>
<td>28</td>
<td>21</td>
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<td>2 step change in classification</td>
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<td>1027</td>
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<td>Davidov [12]</td>
<td>2010</td>
<td>1</td>
<td>331</td>
<td>cytopathologist</td>
<td>Impact of thyroid fine-needle aspiration biopsy on surgical management; retrospective review of patients referred to a high volume referral centre with a thyroid FNA biopsy, compared cytologic diagnoses from center and referring institution using Bethesda System for Reporting Thyroid Cytopathology. Excluded cases with undetermined initial diagnosis ambiguous or incomplete diagnosis, sent for outside opinion/pending consultation, or only a differential diagnosis given</td>
<td>Based on follow-up, the second opinion was correct in 271/394 cases of disagreement (18% of total) including 54 change in management, while the primary pathology was correct in 93/394 cases of disagreement (6.2% of total) including 13 with change in management to less appropriate treatment. Neither was correct in 2.1% of cases (0.8% with treatment change)</td>
<td>Overall</td>
<td>1499</td>
<td>26</td>
<td>5.3</td>
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<td>Non-diagnostic (category I)</td>
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<td>Benign (category II)</td>
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<td>Atypia (category III)</td>
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<td>Suspicious, malignant (category IV)</td>
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<td>1 step change in classification</td>
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<td>Sample Description, Notes</td>
<td>Sample Subtype, Change or Item Compared</td>
<td># Specimens of Subtype</td>
<td>Discrepancy, %</td>
<td>Agreement</td>
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<tr>
<td>Tan (8)</td>
<td>2007</td>
<td>1</td>
<td>147</td>
<td>cytopathologist</td>
<td>routine secondary cytologic review (not blinded) of patients referred to University of California for surgery, initial evaluation at other institutions</td>
<td>patient with preoperative review thyroid gland FNA; excluded patients referred for a second opinion; major = change in surgical management; specificity of FNA interpretation improved from 56 to 76% with review, when compared to final histologic diagnosis (PPV changed from 87 to 93%, NPV 69 to 79%)</td>
<td>overall: benign, indeterminate, suspicious, malignant, nondiagnostic (includes follicular lesions or neoplasms)</td>
<td>147</td>
<td>18</td>
<td>5.4</td>
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<td>Al-Shaikh (2)</td>
<td>2001</td>
<td>1</td>
<td>41</td>
<td>cytopathologist</td>
<td>Blinded reassessment of FNA slides to assess reliability of FNA and FNA findings; FNA slides used mostly in patients with low risk of malignancy</td>
<td>children with single or multiple thyroid nodules who underwent FNA and further management (surgery or follow-up) at The Hospital for Sick Children</td>
<td>overall: classification as benign, malignant, suspicious, insufficient (benign = other benign)</td>
<td>41</td>
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<td>Baloch (3)</td>
<td>2001</td>
<td>1</td>
<td>183</td>
<td>pathologists</td>
<td>interinstitutional: all slides for patients referred to University of Pennsylvania Medical centre for management, compared in-house and submitted diagnosis</td>
<td>thyroid FNA slides</td>
<td>overall: benign, indeterminate, suspicious, malignant, nondiagnostic</td>
<td>183</td>
<td>60</td>
<td>60</td>
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<td>Gerhard (7)</td>
<td>2007</td>
<td>1</td>
<td>95</td>
<td>not stated; original by cytopathologist</td>
<td>blinded FNA cytology review</td>
<td>only considered discordant if noteworthy alteration in clinical management and diagnosis</td>
<td>overall: benign, indeterminate, suspicious, malignant, nondiagnostic</td>
<td>95</td>
<td>24</td>
<td>8</td>
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<tr>
<td>Jean-Gilles (18)</td>
<td>2012</td>
<td>2</td>
<td>192</td>
<td>non-stated; original by cytopathologist</td>
<td>Independent review of 2 , consensus if initially discordant</td>
<td>Patients with histologically confirmed thyroid cancer; 2nd review of cases for which thyroid fine needle aspiration (FNA) previously reported as benign</td>
<td>overall: benign, indeterminate, suspicious, malignant, nondiagnostic</td>
<td>95</td>
<td>24</td>
<td>8</td>
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<tr>
<td>Jing (17)</td>
<td>2012</td>
<td>5-8</td>
<td>50</td>
<td>cytopathologists</td>
<td>Retrospective blinded consensus review of consecutive cases from pathology database, reviewed at multihead microscope, at least 5 reviewers per case</td>
<td>thyroid aspirates previously interpreted as “atypia of undetermined significance/ follicular lesion of undetermined significance” (AUS/FLUS) and followed by surgical interventions</td>
<td>Change in classification: malignant, suspicious, nondiagnostic (includes follicular lesions or neoplasms)</td>
<td>50</td>
<td>78</td>
<td>52</td>
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<td>Duggal (13)</td>
<td>2011</td>
<td>1</td>
<td>74</td>
<td>cytopathologist</td>
<td>comparison of two cytological diagnosis for patients with histologically confirmed thyroid cancer</td>
<td>FNAC thyroid lesions identified as follicular lesions/neoplasms with available surgical resection specimens</td>
<td>FNA, neoplastic diagnosis</td>
<td>74</td>
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### Thyroid – Resection or Sample Type Unknown

<table>
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<tr>
<th>Author</th>
<th>Year</th>
<th># 2nd Reviewers</th>
<th># Specimens</th>
<th>Reviewer (Profession/Training)</th>
<th>Type of Review, Notes</th>
<th>Sample Description, Notes</th>
<th>Sample Subtype, Change or Item Compared</th>
<th># Specimens of Subtype</th>
<th>Discrepancy, %</th>
<th>Agreement %</th>
<th>Kappa</th>
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<tr>
<td>Wang [14]</td>
<td>2011</td>
<td>2</td>
<td>221</td>
<td>expert anatomical pathologists</td>
<td>blinded central review from 23 sites; consensus if initial disagreement</td>
<td>resected thyroid nodules</td>
<td>specific subtype (e.g. follicular adenoma or papillary thyroid cancer)</td>
<td>221</td>
<td>44</td>
<td>56</td>
<td>0.79</td>
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<td>Duggal (13)</td>
<td>2011</td>
<td>2</td>
<td>74</td>
<td>histopathologist</td>
<td>histopathologic diagnoses</td>
<td>surgical resection specimens from cases where FNAC thyroid lesions were identified as follicular lesions/neoplasms</td>
<td>Resection specimens</td>
<td>74</td>
<td>8</td>
<td>92</td>
<td>0.84</td>
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<tr>
<td>Hofman (11)</td>
<td>2009</td>
<td>4</td>
<td>31</td>
<td>pathologists</td>
<td>thyroid tumours initially diagnosed by Pathologists B, C, or D, and reviewed independently by Pathologists A, B, C, and D; thyroidectomy specimens</td>
<td>thyroid tumours of uncertain malignant potential (TT-UMP) including 15 follicular thyroid (FT-UMP) and 16 well-differentiated (WT-UMP); overall concordance (unanimous) = 70%</td>
<td>31</td>
<td>13</td>
<td>87</td>
<td>0.75</td>
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<td>Widder (9)</td>
<td>2008</td>
<td>2+1</td>
<td>185</td>
<td>consensus of pathologist and senior pathology resident; thyroid pathologist for discrepancies</td>
<td>blinded cohort clinical review of thyroid follicular lesions from a single surgeon’s practice. The purpose of this study was to retrospectively re-review all operatively resected follicular lesions over the past decade to determine whether recent histopathologic criteria for the diagnosis of FVPTC would result in a change from the original diagnosis.</td>
<td>H&amp;E slides from patients (age &gt; 18) with diagnosis of follicular adenoma (FA), follicular carcinoma (FC), or follicular variant of papillary thyroid cancer (FVPTC)</td>
<td>185</td>
<td>25</td>
<td>89</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Duggan (10)</td>
<td>2009</td>
<td>46</td>
<td>46</td>
<td>expert in thyroid pathology, not blinded</td>
<td>samples in Widder publication with disagreement sent to international expert</td>
<td>all cases with initial diagnosis of thyroid cancer (states that all lesions already removed)</td>
<td>international expert compared to original diagnosis</td>
<td>46</td>
<td>18</td>
<td>82</td>
<td>0.33</td>
</tr>
<tr>
<td>Hamady (6)</td>
<td>2004</td>
<td>1</td>
<td>66</td>
<td>pathologist with special interest in thyroid disease</td>
<td>retrospective review; cases referred from district general hospitals to Leeds Teaching Hospitals for further management (routine review in all cases, n=49) or expert pathologic opinion (n=17)</td>
<td>all cases with initial diagnosis of thyroid cancer (states that all lesions already removed)</td>
<td>total</td>
<td>66</td>
<td>18</td>
<td>84</td>
<td>0.76</td>
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### Evidence Summary: Head & Neck Cancers

<table>
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<tr>
<th>Author</th>
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<th>Specimens</th>
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<th># Specimens of Subtype</th>
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<td>Franc (5)</td>
<td>2003</td>
<td>6</td>
<td>324</td>
<td>consensus of 6 pathologists</td>
<td>histological review; comparison of original diagnosis and diagnosis reached during consensus conference 1980-99</td>
<td>thyroid carcinoma cases randomly selected from files of the National Cancer Registry of Belarus and Database of the Ukrainian National Cancer Registry</td>
<td>• overall (benign, malignant, or doubtful)opathic review; comparison of original diagnosis and diagnosis reached during consensus conference 1980-99</td>
<td>324</td>
<td>7</td>
<td>93</td>
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<td>Lange (4)</td>
<td>2001</td>
<td>4</td>
<td>232</td>
<td>pathologists</td>
<td>reference diagnosis by four experienced pathologists compared to primary diagnosis</td>
<td>thyroid tumors operated 1985-98 diagnosis of cancer ↔ benign follicular carcinoma</td>
<td></td>
<td>197</td>
<td>18</td>
<td>82</td>
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<tr>
<td>Abbey (20)</td>
<td>1995</td>
<td>6</td>
<td>120</td>
<td>oral pathologists</td>
<td>interinstitutional: blind review compared with sign-out diagnoses (determined by consensus of 4 or 5 board-certified oral pathologists)</td>
<td>selected slides of oral biopsies exhibiting hyperkeratosis (n=20) or epithelial dysplasia (40 mild, 41 moderate, 19 severe); reviewers graded each as mild, moderate, severe, or no epithelial dysplasia</td>
<td>pathologist 1 overall</td>
<td>120</td>
<td>44</td>
<td>56</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2+ step discrepancy presence/absence of dysplasia</td>
<td></td>
<td>7</td>
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<tr>
<td>Westra (21)</td>
<td>2002</td>
<td>1 (+panel)</td>
<td>814</td>
<td>pathologists with broad expertise in surgical pathology</td>
<td>interinstitutional: mandatory second opinion at Johns Hopkins Hospital Department of Otolaryngology-Head and Neck Surgery for all patients referred for therapy based on diagnosis of outside pathologist; discrepancies reviewed by panel of 7+ pathologists</td>
<td>discrepant diagnosis defined as change resulting in modification in therapy or prognosis; major change in treatment; follow-up supported 2nd opinion in 41/43 cases</td>
<td>overall</td>
<td>814</td>
<td>6.6</td>
<td>6.0</td>
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<td># Specimens of Subtype</td>
<td>Discrepancy, %</td>
<td>Agreement % Kappa</td>
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<tr>
<td>Fischer (22)</td>
<td>2004</td>
<td>2</td>
<td>87</td>
<td>pathologists; head and neck, oral and maxillofacial</td>
<td>comparison between classification of local pathologist and 2 pathologists at central pathology lab of multicenter study, independent assessment, blinded to clinical findings</td>
<td>clinically suspicious oral lesions biopsied from patients (age &gt; 18) with previous upper aerodigestive tract carcinoma (UADT)</td>
<td>overall: no abnormality, hyperplasia/hyperkeratosis, tongue, gingiva and hard palate, buccal mucosa and vestibule</td>
<td>87 51 44 25 18 21</td>
<td>49 45 52 0.62 0.42 0.68</td>
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<td>Pentenero (23)</td>
<td>2003</td>
<td>1</td>
<td>46</td>
<td>pathologists; general histopathologic and oral experience</td>
<td>retrospective study; blinded review of all pathology slides from oral potentially malignant lesions (PML). Comparison of provisional and final diagnoses</td>
<td>incisional biopsy and resection specimens from patients with oral PML (potentially malignant lesions) diagnosed as moderate to severe dysplasia or in situ carcinoma</td>
<td>overall: no or mild dysplasia vs. moderate or severe dysplasia vs. carcinoma</td>
<td>46 22</td>
<td>78 0.76</td>
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<td>Kurtz (24)</td>
<td>2005</td>
<td>panel</td>
<td>40</td>
<td>pathologists</td>
<td>retrospective: re-review of perineural and vascular invasion cases, and review of slides using IHC</td>
<td>oral cavity squamous cell carcinoma in which the status of perineural and vascular invasion had been part of the original pathology report</td>
<td>Perineural invasion: original vs. review, original vs. final (review + IHC), review vs. review + IHC</td>
<td>40 33 40 40 40 40</td>
<td>67 47 75</td>
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<td>Kammerer (25)</td>
<td>2013</td>
<td>2</td>
<td>80</td>
<td>pathologists</td>
<td>Evaluation of oral brush biopsies, blinded prospective trial</td>
<td>Clinically suspicious by not evidently malignant oral lesions; only review of false negative cytology when compared to histology</td>
<td>Perineural invasion: original vs. review, original vs. final (review + IHC), review vs. review + IHC</td>
<td>14 14</td>
<td>86</td>
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<td>Lind (26)</td>
<td>1995</td>
<td>1</td>
<td>77</td>
<td>pathologists</td>
<td>peer review after 1st pathologist finished report; exclude cases where could not reach consensus</td>
<td>all diagnostic surgical pathology biopsies; major error=clinically significant; minor=no treatment change</td>
<td>head and neck</td>
<td>77 2.6 0</td>
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<tr>
<td>Kronz (27)</td>
<td>1999</td>
<td>1</td>
<td>200</td>
<td>mandatory 2nd opinion; all cases referred to treating institution, excludes consult cases with uncertain diagnosis</td>
<td>major modification in therapy or prognosis, does not include change only in histologic grade or stage, limited number of cases as most were seen by the dermatology department</td>
<td>ear, nose, throat</td>
<td>200 1.0 99</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Layfield (28)</td>
<td>2002</td>
<td>1</td>
<td>14</td>
<td>review of outside cytology material</td>
<td></td>
<td>thyroid</td>
<td>14 28 21 7 72</td>
<td></td>
<td></td>
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<tr>
<td>Weir (29)</td>
<td>2003</td>
<td>1</td>
<td>93</td>
<td>interinstitutional, at request of clinical staff or treating institution</td>
<td>compared 1st and treating institution reports; major=clinical impact</td>
<td>Histological: head and neck</td>
<td>80 13 1.3 2.5 15</td>
<td></td>
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<td></td>
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<tr>
<td>Ahmed (30)</td>
<td>2004</td>
<td>1</td>
<td>27</td>
<td>2nd opinion at major referral centre</td>
<td>reviewed at Aga Khan University, Pakistan; most sent by clinicians, some by primary pathologists</td>
<td>head and neck</td>
<td>27 44 56</td>
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**Studies that reported on several cancer sites**

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<th>Author</th>
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<th># 2nd Reviewers</th>
<th># Specimens</th>
<th>Reviewer (Profession/Training)</th>
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<th>Sample Description, Notes</th>
<th>Sample Subtype, Change or Item Compared</th>
<th># Specimens of Subtype</th>
<th>Discrepancy, %</th>
<th>Agreement % Kappa</th>
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<tr>
<td>Lind</td>
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<td>1</td>
<td>77</td>
<td>pathologists</td>
<td>peer review after 1st pathologist finished report; exclude cases where could not reach consensus</td>
<td>all diagnostic surgical pathology biopsies; major error=clinically significant; minor=no treatment change</td>
<td>head and neck</td>
<td>77 2.6 0</td>
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<td>Kronz</td>
<td>1999</td>
<td>1</td>
<td>200</td>
<td>mandatory 2nd opinion; all cases referred to treating institution, excludes consult cases with uncertain diagnosis</td>
<td>major modification in therapy or prognosis, does not include change only in histologic grade or stage, limited number of cases as most were seen by the dermatology department</td>
<td>ear, nose, throat</td>
<td>200 1.0 99</td>
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<td>Layfield</td>
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<td>review of outside cytology material</td>
<td></td>
<td>thyroid</td>
<td>14 28 21 7 72</td>
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<tr>
<td>Weir</td>
<td>2003</td>
<td>1</td>
<td>93</td>
<td>interinstitutional, at request of clinical staff or treating institution</td>
<td>compared 1st and treating institution reports; major=clinical impact</td>
<td>Histological: head and neck</td>
<td>80 13 1.3 2.5 15</td>
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<td>Ahmed</td>
<td>2004</td>
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<td>27</td>
<td>2nd opinion at major referral centre</td>
<td>reviewed at Aga Khan University, Pakistan; most sent by clinicians, some by primary pathologists</td>
<td>head and neck</td>
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<td>Discrepancy, %</td>
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<tr>
<td>Tsung</td>
<td>2004</td>
<td>1</td>
<td>75</td>
<td>pathologists</td>
<td>patients referred to cancer center for therapy or second opinion; all cases referred to treating institution</td>
<td>major discrepancies (benign to malignant or vice versa), different type of neoplasm, change in N or M of TNM classification</td>
<td>salivary gland</td>
<td>oral cavity</td>
<td>thyroid</td>
<td>15</td>
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<td>Raab</td>
<td>2005</td>
<td>1</td>
<td>170</td>
<td>pathologist</td>
<td>review after sign-out conferences, external review, internal QA, physician request; self-report of 100 consecutive specimens at 74 institutions</td>
<td>pharynx</td>
<td>salivary gland</td>
<td>141</td>
<td>29</td>
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<tr>
<td>Renshaw</td>
<td>2006</td>
<td>1</td>
<td>168</td>
<td>pathologist</td>
<td>internal blinded rapid review; 1/6 of cases from new pathologists, rest random</td>
<td>major error leads to amendment, minor error requires no action</td>
<td>head and neck, all discrepancies</td>
<td>thyroid gland</td>
<td>168</td>
<td>0</td>
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<tr>
<td>Lu</td>
<td>2009</td>
<td>1</td>
<td>231</td>
<td>pathologist</td>
<td>external consultation</td>
<td>thyroid gland</td>
<td>salivary gland</td>
<td>173</td>
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<td>Bomeisl</td>
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<td>1</td>
<td>379</td>
<td>pathologist</td>
<td>interinstitutional consultation, FNA, prior to treatment or patient requested 2nd opinion</td>
<td>thyroid glands</td>
<td>change in management or therapy neck: lymph nodes and soft tissue</td>
<td>173</td>
<td>136</td>
<td>16.2</td>
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Abbreviations: AUS=atypia of undetermined significance; FNA=fine needle aspiration; FNAC=fine needle aspiration cytology; IHC=immunohistochemistry; SFM=suspicious for malignancy; SFN=suspicious for follicular or Hurthle cell neoplasm.
DISCUSSION
An initial (primary) pathology review should include synoptic reporting, as stipulated in the CAP protocols (see http://www.cap.org) and based on the American Joint Commission on Cancer (AJCC) standards (44). CCO and the APC have endorsed the CAP cancer checklists as the content standard for pathology reporting (45,46). Synoptic reporting can help ensure that reports are complete, and in Ontario such reports are currently required for incisional/excisional biopsy and resections of the larynx (supraglottis, glottis, subglottis), lip and oral cavity, major salivary glands, nasal cavity and paranasal sinuses, pharynx (oropharynx, hypopharynx, nasopharynx), resection specimens of the thyroid gland, and biopsy and resections of ocular adnexa (46).

CCO PEBC Guideline #5-3 on the management of head and neck cancer (36) also advised use of the CAP-CCO standards for reporting head and neck malignancies and recommended that histopathology reporting of specimens from the primary site of head and neck cancer include tumour site, tumour grade, tumour type, maximum tumour dimension, maximum depth of invasion, margin involvement by invasive and/or severe dysplasia and margin dimensions, pattern of infiltration, perineural involvement, and lymphatic/vascular permeation. The reporting of nodal dissections should include a description of the levels and structures included in the specimen, including the number of involved and uninvolved nodes, the level of these nodes, and the presence and location of extracapsular spread of tumour.

CCO PEBC Guideline #5-9 on human papilloma virus (HPV) testing in head and neck cancer (47), as well as several other guidelines (48), indicate that suspected or diagnosed oropharyngeal squamous cell carcinomas should be routinely tested for HPV status (p. 16). The PEBC guideline recommends the use of immunohistochemistry (IHC), with additional testing by polymerase chain reaction (PCR) or in situ hybridization (ISH), especially for high-risk HPV subtypes. Epstein Barr Virus (EBV) may correlate highly with a nasopharyngeal site (42), and suspected or diagnosed nasopharyngeal cancers should be tested for EBV. Unknown primary head and neck cancers should be tested for HPV and EBV. HPV and EBV test results often change treatment for patients, and these tests should be standard practice.

Most of the studies in Table 1 deal with thyroid specimens, either by FNA or resection, with a smaller number of studies on oral cancers. The area of practice of the primary pathologist is not specified for most studies but is assumed to be general anatomic pathology or cytology (not an expert in head and neck pathology). The qualifications/specialty of the secondary review pathologist are noted in the table when reported in the publications. The secondary review is often an interinstitutional review at the treating centre, and in these studies, the review is assumed to be by a pathologist/cytopathologist with expertise in the relevant area of head and neck pathology. They did not directly address who should perform the secondary review; however, it is noted that the PEBC (36) and NICE (37,38) guidelines recommend that care should be coordinated by a team including pathologists with expertise in histopathology and cytopathology. Several guidelines recommend thyroid cancer specimens be reviewed by pathologists with special interest or expertise in thyroid cancer (37-42). The authors agree that review of head and neck pathology specimens should be performed by a pathologist with expertise in head and neck surgical pathology or cytopathology or relevant subspecialty (e.g., thyroid, endocrine tumours). In Ontario most secondary review will be in cancer centres where pathology specialization occurs.

Discrepancy rates reported in most studies are relatively high, though not all discrepancies are clinically relevant, as can be seen from the papers that make this distinction. The authors attempted to judge the clinical relevance of discrepancies in evaluating the studies and developing conclusions.
A. Thyroid - Fine Needle Aspiration (FNA)

Accurate diagnosis of anaplastic carcinoma, medullary carcinoma, and non-epithelial cancers (lymphoma, sarcoma) is important as their treatments are different. While no studies were located in the review, these cancers are relatively rare, and a general pathologist may not encounter sufficient specimens to be able to diagnose them. Review should be by a pathologist with expertise in these areas. Sample initially reported as non-diagnostic may change on secondary review, but a large portion will still be non-diagnostic. Resampling, when feasible, may be more efficient than routine secondary review. Samples diagnosed as suspicious for neoplasm or malignancy had very high discrepancy rates. As treatment would still be surgery, with pathology review of resection specimens, routine secondary review of FNA specimens is not required.

Papillary thyroid cancer is the most common variant and had much lower discrepancy rates than those for follicular neoplasms. The consensus of the authors is that routine secondary review is not required because diagnosis would need to be downgraded by three categories in order to change management, and, therefore, any change in treatment based on secondary pathology review is unlikely.

B. Thyroid Biopsy

Biopsies of the thyroid are not usually performed except for an enlarging mass suspicious for anaplastic thyroid cancer (especially in older individuals) or for rapidly progressing lymphoma. Differentiating between lymphoma and anaplastic thyroid cancer is essential. As surgery is usually not feasible, there will be no further pathology specimens prior to treatment (e.g., chemotherapy, radiotherapy), and the diagnosis should be confirmed by secondary pathology review. Treatment is often urgent, and clinical judgement will be required in deciding whether to start treatment based on clinical presentation prior to the completion of pathology review.

C. Hemithyroidectomy/Total Thyroidectomy

In the case of hemithyroidectomy, the results of the pathologic assessment will determine whether more surgery (i.e., total thyroidectomy) is required. One study on thyroid resection found the secondary review resulted in an 18% change in prognosis and/or therapy (6). Other studies reported 7% to 18% discrepancy rates between benign and malignant diagnoses and for subtype. One study reported that samples diagnosed as follicular carcinoma had a discrepancy rate of 73% compared to 4% for papillary carcinoma (5). Widder et al. (9) reported a 25% change between benign and malignant for cases diagnosed as follicular adenoma, follicular carcinoma, or follicular variant of papillary thyroid cancer. The data, along with the authors’ experience, suggest the benefit of secondary review of hemithyroidectomy or total thyroidectomy specimens with diagnoses of medullary thyroid cancer; of follicular lesions/neoplasms suspicious for vascular invasion or capsular extension or with suspicious nuclear features; and of aggressive subtypes of papillary thyroid carcinoma. Routine secondary pathology review of thyroidectomy specimens is not required for other papillary or anaplastic cancers.

D. Mucosal (Mouth, Larynx, Oral Cavity, Tonsil) and Sinonasal Tract Biopsies

Mucosal melanoma, atypical melanocytic lesions, non-epithelial malignancies including lymphoma and sarcoma, and salivary gland malignancy are rarer cancers that general pathologists are unlikely to encounter routinely. Secondary pathology review is therefore warranted. Secondary pathology review is also recommended for biopsies of mucosal and sinonasal tract lesions assessed as moderate or severe (high-grade) dysplasia or carcinoma in

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situ (CIS) but is not required as routine practice for lesions assessed as mild or low-grade dysplasia.

E. Mucosal Resections

The literature review did not include any studies on discrepancy rates for secondary pathology review of mucosal resections. Current practice is that mucosal resections are usually done by head and neck surgeons at cancer centres, and the initial review of specimens is performed by pathologists with expertise in this area. Secondary review is usually required only if elements of the pathology report are missing.

F. Salivary Gland - Resection

The literature review did not include any studies on discrepancy rates for secondary pathology review of salivary gland resections. While there are four common types of salivary gland malignancies, secondary review will not usually affect treatment and, therefore, routine review is not required, as is consistent with current practice.

G. Parathyroid

No studies on parathyroid cancer were included in the literature review. Current practice in Ontario is not to conduct routine secondary review.

CONCLUSIONS
A. Thyroid - Fine Needle Aspiration (FNA)

Anaplastic carcinoma, medullary carcinoma, and non-epithelial cancers (lymphoma, sarcoma) should have secondary pathology review. Routine secondary pathology review is not required for papillary thyroid cancer or specimens suspicious for neoplasm or malignancy. Resampling may be appropriate for non-diagnostic specimens; however, routine secondary review is not necessary.

B. Thyroid Biopsy

Thyroid biopsies should have secondary pathology review.

C. Hemithyroidectomy / Total Thyroidectomy

Hemithyroidectomy or total thyroidectomy specimens should have secondary pathology review if there is a diagnosis of medullary thyroid cancer; follicular lesions/neoplasms suspicious for vascular invasion or capsular extension or with suspicious nuclear features; or aggressive subtypes of papillary thyroid carcinoma. Routine secondary pathology review of thyroidectomy specimens is not required for papillary or anaplastic cancers (other than aggressive subtypes as indicated above).

D. Mucosal (Mouth, Larynx, Oral Cavity, Tonsil) and Sinonasal Tract Biopsies

Mucosal and sinonasal tract biopsies with diagnoses of mucosal melanoma; atypical melanocytic lesions; non-epithelial malignancies including lymphoma and sarcoma; and salivary gland malignancy should have secondary pathology review. Lesions assessed as moderate or severe (high-grade) dysplasia or CIS should also have secondary review. Routine secondary pathology review is not required for biopsies of mucosal and sinonasal tract lesions assessed as mild or low-grade dysplasia.
E. Mucosal Resections
   Routine secondary pathology review is not required for mucosal resection specimens as initial review is usually by pathologists with expertise in this area.

F. Salivary Gland - Resection
   Routine secondary review of salivary gland resection specimens is not required as the treatment is the same for all major subtypes.

G. Parathyroid
   Based on current practice, routine secondary pathology review is not required for parathyroid specimens.

RELATED PEBC GUIDELINES


UPDATING
This series of evidence summaries on secondary pathology review will be considered current for three years. The evidence summaries will then be designated as archived and indicated as such on the CCO website. These reports will not undergo annual assessment. They will not be updated unless required as the basis of a new guideline by the Pathology and Laboratory Medicine Program (PLMP).

CONFLICT OF INTEREST
In accordance with the PEBC Conflict of Interest (COI) Policy, the authors and internal and external reviewers were asked to disclose potential COIs. For the Working Group, potential COIs that were declared are summarized in Appendix I. The COIs declared did not disqualify any individuals from performing their designated role in the development of this review, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi.mcmaster.ca.
ACKNOWLEDGEMENTS AND AUTHORSHIP

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A complete list of the members of the Best Practices for Oncologic Pathology Secondary Review: Head and Neck Cancers Working Group with their affiliations and conflict of interest information is provided in Appendix 1.

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No conflicts of interest were declared by the Working Group members.
Appendix II. Reproducibility studies (data not extracted).

Thyroid


Other


