Evidence Summary #22-2-2

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

Best Practices for Oncologic Pathology Secondary Review: Gastrointestinal 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
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#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

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822   Fax: 905 526-6775   E-mail: ccopgi@mcmaster.ca
QUESTION
What types of specimens suspected to be or diagnosed as gastrointestinal cancer should or should not have routine secondary pathology review?

INTRODUCTION
This report is part of a series of reports on pathology secondary 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 gastrointestinal pathology.

METHODS
The evidence-based reports developed by the Cancer Care Ontario (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 GF of the PEBC.

The body of evidence in this review is primarily comprised of comparative studies on interobserver accuracy or agreement. The systematic review and companion recommendations are 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 usually initiated at the request of the patient or treating clinician, multidisciplinary case conference (MCC) process, or 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 (NZZG), 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 gastrointestinal cancer or aspects of cancer such as

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

RESULTS

For gastrointestinal cancers (esophageal, colorectal, and gastric cancers, as well as cancers of the liver and pancreas), the search resulted in 103 articles, of which 68 were reproducibility studies. The 35 studies on gastrointestinal cancer (2-36) that report agreement or disagreement between the initial and secondary pathology review are summarized in Table 1. There are an additional 12 studies that include gastrointestinal cancer along with other cancers (37-49). The study by Ahmed et al (42) reported a discrepancy rate of 33% but included samples submitted at the request of the primary pathologist. Rates in the other large studies (> 100 samples) were 1.2% to 6% for all discrepancies and 0.9% to 3% for major discrepancies (37,39,41,43-46,49). 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. Esophageal Cancer

The study by Peng et al (2) reviewed false-negative brush cytology and mucosal biopsy samples from patients with adenocarcinoma of the esophagus or esophagogastric junction who underwent preoperative chemoradiation. The false-negative results for brush cytology samples were 40%; pathologic review indicated that pathology misinterpretation was the cause of 30% of the error in the samples reviewed, which would be equivalent to interpretation error in 12% of brush biopsy samples. For mucosal biopsy, accuracy was 36%, and interpretation error accounted for only 2% of the false-negative results.

The rest of the studies involve patients with Barrett’s esophagus. Studies are on the diagnosis, dysplasia grade, or presence of intestinal metaplasia (IM). Lorinc et al (6) reported a diagnostic discrepancy rate of 4% to 12% with hematoxylin and eosin (H&E) staining. Agreement on dysplasia presence and type for three review pathologists increased from kappa =0.24 using H&E to kappa=0.72 with p53 immunohistochemistry (IHC). Two large studies (7,9) report 3% and 12% discrepancy rates for identifying the presence of IM, while several studies report discrepancy rates in grade of dysplasia of 28% to 90%. Yerian (50) reviews the histology in Barrett’s esophagus and concludes that the diagnosis of dysplasia should be confirmed by a pathologist experienced in Barrett’s esophagus before aggressive therapy is contemplated.

The study by Stolte et al (11), in which a secondary review was performed by a pathologist with considerable experience in Barrett’s diagnostics, found that 15% of specimens with initial diagnosis of high-grade intraepithelial neoplasia (HGIEN) had no IEN on review, and secondary review would thus avoid overtreatment in these patients. A higher portion (77%) of HGIEN had a review diagnosis of cancer, though this is considered less clinically relevant as both lead to treatment. Hulscher et al (4) reported 28% discrepancy in high-grade dysplasia, of which all were considered minor (affecting follow-up but not immediate therapy).

For low grade dysplasia, some studies (3,7) found that a GI specialist did not perform better than a general pathologist, though Pech et al (8) reported less disagreement for GI pathologists (18% versus 50%). Two large studies (7,9) report 3% and 12% discrepancy on presence of IM, while several studies report discrepancy in the grade of dysplasia of 28% to 90%. Hulscher et al (4) indicated 90% discrepancy in low-grade dysplasia diagnoses, but all discrepancies were considered minor (affecting follow-up but not immediate therapy).
Table 1. Pathologic discrepancy rates between primary and secondary review pathologists: gastrointestinal cancer. (Note: for ease of reading, a suggestion is to 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>
<th>Kappa</th>
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</thead>
<tbody>
<tr>
<td>Peng (2)</td>
<td>2009</td>
<td>2</td>
<td>67</td>
<td>pathologists</td>
<td>review of false negative brush cytology samples</td>
<td>patients with esophageal or esophagogastric junction (EGJ) adenocarcinoma who underwent preoperative combination chemoradiation (CRT)</td>
<td>false negative cases, discrepancy due to interpretation brush cytology mucosal biopsy</td>
<td>27</td>
<td>30</td>
<td>70</td>
<td>98</td>
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<tr>
<td>Skacel (3)</td>
<td>2000</td>
<td>3</td>
<td>43</td>
<td>GI pathologists</td>
<td>blind review to determine variability of low grade dysplasia diagnosis</td>
<td>patients with Barrett’s esophagus, 43 samples originally coded as low-grade dysplasia (LGD) plus 57 others for blinding purposes</td>
<td>original diagnosis of low grade dysplasia Pathologist GI-1 Pathologist GI-2 Pathologist GI-3</td>
<td>43</td>
<td>70</td>
<td>56</td>
<td>16</td>
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<tr>
<td>Hulscher (4)</td>
<td>2001</td>
<td>1</td>
<td>30</td>
<td>2nd opinion at specialized diagnosis /treatment centre</td>
<td>reassessment, including IHC, of biopsies diagnosed as Barrett’s esophagus; major changed therapy, minor affects follow-up grade of dysplasia high grade dysplasia low grade dysplasia</td>
<td>30</td>
<td>18</td>
<td>28</td>
<td>50</td>
<td>72</td>
<td>10</td>
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<tr>
<td>Baak (5)</td>
<td>2002</td>
<td>1</td>
<td>143</td>
<td>pathologist with special GI interest</td>
<td>consecutive biopsies</td>
<td>comparison of dysplasia grades in Barrett’s esophagus</td>
<td>grade of dysplasia high grade dysplasia low grade dysplasia indefinite no dysplasia</td>
<td>143</td>
<td>35</td>
<td>52</td>
<td>7</td>
</tr>
<tr>
<td>Lorinc (6)</td>
<td>2005</td>
<td>3</td>
<td>115</td>
<td>pathologists: 1 special interest in GI, 1 resident, 1 from county hospital</td>
<td>blinded comparison, evaluation of IHC</td>
<td>biopsies diagnosed as Barrett’s esophagus stained with H&amp;E were compared to original diagnosis, and reevaluated for dysplasia using p53 and Ki67 IHC. Kappa for the 3 pathologists (dysplasia presence and type) increased from 0.24 using H&amp;E to 0.72 with p53 IHC</td>
<td>diagnosis of Barrett’s esophagus (H&amp;E only) Observer 1 Observer 2 Observer 3</td>
<td>115</td>
<td>91</td>
<td>91</td>
<td>88</td>
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<tr>
<td>Kerkhof (7)</td>
<td>2007</td>
<td>1</td>
<td>920</td>
<td>expert GI pathologists</td>
<td>blinded review by expert in trial to determine follow-up frequency</td>
<td>biopsy specimens from patients with Barrett’s esophagus</td>
<td>presence of intestinal metaplasia (IM) patients with IM: grade of dysplasia first pathologist was non-expert first pathologist was expert</td>
<td>920</td>
<td>97</td>
<td>97</td>
<td>72</td>
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<td>Pech (8)</td>
<td>2007</td>
<td>2</td>
<td>50</td>
<td>specialized GI pathologists</td>
<td>consecutive patients, reviewed in blinded fashion</td>
<td>initial diagnosis of low grade intraepithelia neoplasia (LGIN) in Barrett’s esophagus; reclassified as no neoplasia, LGIN, HGIN, Barrett’s carcinoma</td>
<td>original diagnosis of low grade dysplasia pathologist 1 (general) vs. final consensus pathologist 1 vs. pathologist 2 (specialist) pathologist 1 vs. pathologist 3 (specialist) pathologist 2 vs. pathologist 3</td>
<td>50 50 70 76 18</td>
<td>30 24 -0.17 24 -0.17</td>
<td>0.69</td>
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<tr>
<td>Corley (9)</td>
<td>2009</td>
<td>1</td>
<td>616</td>
<td>pathologist</td>
<td>slide review</td>
<td>Barrett’s esophagus: reproducibility of esophageal intestinal metaplasia diagnosis presence of intestinal metaplasia (IM) initial diagnosis of intestinal metaplasia original diagnosis of gastric or columnar metaplasia</td>
<td>616 580 12 12</td>
<td>88 88 86 0.42</td>
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<td>Sonwalkar (10)</td>
<td>2010</td>
<td>3</td>
<td>41</td>
<td>experienced histopathologists</td>
<td>interobserver variation in indefinite dysplasia (IND) in Barrett’s esophagus; 61 IND slides (41 patients) and 60 other slides original diagnosis of indefinite dysplasia histopathologist P1 histopathologist P2 histopathologist P3</td>
<td>41 66 93 71</td>
<td>34 7 29</td>
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<td>Stolte (11)</td>
<td>2012</td>
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<td>275</td>
<td>Pathologist with considerable experience in Barrett’s diagnostics</td>
<td>Second opinion review; checked by follow-up in 75% of patients</td>
<td>Primary diagnosis of high grade intraepithelial neoplasia (HGIE) in Barrett’s esophagus HGIE → no IEN HGIE → LGIEN HGIE → Barrett Ca 2nd review compared to follow-up diagnosis</td>
<td>275 207 93 15 1 77 16</td>
<td>7 85 99 23</td>
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<td>Colquhoun (14)</td>
<td>2003</td>
<td>3</td>
<td>190</td>
<td>histopathologists, expert in field of anorectal pathology</td>
<td>representative samples of entire spectrum of anal dysplasia Severity of anal dysplasia Pathologist 1 Pathologist 2 Pathologist 3 Complete agreement, original and reviewers</td>
<td>68</td>
<td>0.38 0.48 0.60</td>
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<td>Colorectal</td>
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<td>Non adenomatous polyps Adenomas adenomatous nature histological type (tubular, tubulo-villous, villous) degree of dysplasia (mild, moderate, severe, carcinoma in situ) degree of dysplasia (low or high) histological type + degree of dysplasia</td>
<td>71 255 255 255 255</td>
<td>15 4 4 44 20</td>
<td>96 67 56 80 80</td>
<td>0.67 0.46 0.26 0.34 0.34</td>
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<td>Terry (13)</td>
<td>2002</td>
<td>1</td>
<td>318</td>
<td>pathologists</td>
<td>central review compared to community pathologists</td>
<td>colorectal adenomatous polyp cases from colonoscopy-based case-control study</td>
<td>histological type degree of dysplasia (5 categories) degree of dysplasia (high versus low grade)</td>
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<td>71</td>
<td>pathologists</td>
<td>central review vs. diagnosis from 4 study sites using uniform pathology criteria</td>
<td>advanced adenomas initially diagnosed in endoscopy based case-control studies of adenomatous polyps</td>
<td>initial diagnosis of severe dysplasia or carcinoma in situ</td>
<td></td>
<td>18</td>
<td>82</td>
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<td>Komuta (15)</td>
<td>2004</td>
<td>3</td>
<td>88</td>
<td>experienced gastrointestinal pathologists</td>
<td>slides reviewed in blinded fashion, unaware of initial or each other's results</td>
<td>endoscopic removal of malignant polyps</td>
<td>• malignant colorectal polyps identified as carcinoma in situ on review</td>
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<td>• T stage (depth of tumour)</td>
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<td>0.52</td>
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<td>• resection margin status</td>
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<td>• Level of invasion (Haggitt's classification)</td>
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<td>• histology grade (well vs. moderately differentiated)</td>
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<td>Denis (16)</td>
<td>2009</td>
<td>2</td>
<td>300</td>
<td>expert GI pathologists</td>
<td>blind to original diagnosis and other expert; 155 slides needed joint exam to reach consensus</td>
<td>colorectal polyps detected by fecal occult blood test colorectal cancer screening; included all serrated adenomas (71), Tis (77) and T1 carcinomas (39), rest random (114). [comment: inconsistencies between table and text]</td>
<td>benign polyps malignant polyps histological type serrated adenoma degree of dysplasia histological type + degree of dysplasia diagnosis extrapolated to all screened polyps</td>
<td>261</td>
<td>65</td>
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<td>2560</td>
<td>55</td>
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<td>Bustamante-Balen (17)</td>
<td>2009</td>
<td>1</td>
<td>195</td>
<td>pathologists, special interest in GI</td>
<td>unaware of previous diagnosis</td>
<td>187 hyperplastic polyps (Hp) and 7 serrated adenomas (Sa) from colonoscopies; reevaluated as Hp, Sa, traditional serrated adenoma (TSA), sessile serrated adenoma (SSA). [inconsistencies and missing data]</td>
<td>type/subtype of hyperplastic polyps Pathologist 1 Pathologist 2</td>
<td>142</td>
<td>45</td>
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<td>183</td>
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<td>Khalid (18)</td>
<td>2009</td>
<td>3</td>
<td>40</td>
<td>GI pathologists</td>
<td>diagnosis in 2001, review in 2007; aware of original diagnosis</td>
<td>consecutive proximal colon polyps ≥ 5 mm in size originally interpreted as hyperplastic polyps</td>
<td>hyperplastic changed to sessile serrated adenoma Pathologist A Pathologist B Pathologist C</td>
<td>43</td>
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<td>85</td>
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<td>Lu (19)</td>
<td>2010</td>
<td>3</td>
<td>1402</td>
<td>GI subspecialist or special interest</td>
<td>search for sessile serrated adenomas</td>
<td>colorectal polyps biopsied endoscopically with original diagnosis of hyperplastic polyps (Hp); cases reclassified as sessile serrated adenomas (SSA) were studied</td>
<td>hyperplastic changed to sessile serrated adenoma (other changes not recorded)</td>
<td>1402</td>
<td></td>
<td>5.8</td>
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</table>
| van Putten      | 2011 | 1               | 440         | expert pathologist            | first evaluated by either a general or expert pathologist, then reevaluated by expert pathologist | randomly selected polyps from Dutch randomized population-based colorectal cancer screening programme (CORERO 1) | • adenomatous or non-adenomatous nature  
  • initially by general pathologist  
  • initially by expert pathologist  
  • adenomas: non-advanced vs. advanced  
  • initially by general pathologist  
  • initially by expert pathologist  
  • low-grade vs. high-grade dysplasia  
  • tubular/tubulo-villous vs. villous adenoma | 440  
 324  
 116  
 322  
 230  
 92  
 322  
 315  |
| Kennecke        | 2012 | 1               | 38          | pathologist                   | clinical drug trial: central pathology review after review at the local institution | patients with locally advanced or low rectal cancer stage II-IV; surgical specimens after neoadjuvant chemotherapy and radiation. Major discrepancy affected the primary endpoint (pCR rate) | tumour stage | 38  
 16  
 8  |
| Huang           | 2013 | 2               | 95          | Gastrointestinal pathologists | Retrospective review, WHO classification criteria, 2006-2010, originally diagnosed by several pathologists in both academic and community hospitals | Rectal polyps diagnosed originally as sessile serrated adenoma (SSA), serrated polyp, or hyperplastic polyp (HP) with features of SSA | • SSA → other (HP-P or HP)  
  • HP with features of SSA → HP, HP-P, inflammatory-type polyp, SA unclassifiable  
  • SSA or HP + SSA features → HP-P | 26  
 52  
 78  |
| Hahm            | 2001 | 1               | 106         | GI pathologist               | review at request of treating physicians; exclude 2nd opinion requested by referring pathologist | All discrepant diagnoses were reviewed by a 3rd pathologist; major =significant change in therapy or prognosis; minor=minimal change | gastrointestinal, other than liver missing or unclear information diagnostic disagreement | 106  
 18  
 15  
 8  |
| Piaton          | 2011 | 1               | 1223        | Academic cytopathologist (control reader) aware of specimen type but blinded to previous diagnosis; panel of 7 cytopathologists | Local readers (primary review) then control reader blinded to previous diagnosis; discordant cases, concordant positive results, and random selection of negative concordant cases reviewed jointly by panel of 7 cytopathologists (final diagnosis) | Study on detection of intraperitoneal free cancer cells (IFCCs) from serous fluids in patients undergoing surgery for non-gynecologic peritoneal adenocarcinomas previously ascertained by histopathology; excluded primary peritoneal malignancies (malignant mesothelioma and pseudomyxoma peritonei) or benign tumours | local vs control reader  
  benign, malignant, dubious categories  
  dubious/negative vs others  
  local vs final (panel)  
  dubious/negative vs others | 1223  
 272  |
<table>
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<th>Author</th>
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<th># 2nd Reviewers</th>
<th># Specimens</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 %</th>
<th>Kappa</th>
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<tbody>
<tr>
<td>Plummer (25)</td>
<td>1997</td>
<td>2</td>
<td>50</td>
<td>pathologist</td>
<td>chemoprevention trial on stomach cancer</td>
<td>biopsy of precancerous stomach lesions; stratified random sample with 10 subjects each for 5 diagnostic categories based on original diagnosis</td>
<td>Pathologist X vs baseline (Y or Z) Pathologist Y vs baseline (X or Z) Pathologist X vs Y on review intestinal metaplasia superficial, chronic or atrophic gastritis</td>
<td>32</td>
<td>42</td>
<td>59</td>
<td>78</td>
</tr>
<tr>
<td>Muehldorfer (26)</td>
<td>2002</td>
<td>1</td>
<td>21</td>
<td>pathologist</td>
<td>prospective study; review by reference pathologist</td>
<td>hyperplastic gastric polyps; review of samples with relevant diagnostic difference between biopsy and polypectomy or focal carcinomas</td>
<td>histological classification, biopsy + polypectomy samples</td>
<td>32</td>
<td>49</td>
<td>76</td>
<td>92</td>
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<tr>
<td>Sarela (27)</td>
<td>2005</td>
<td>3</td>
<td>22</td>
<td>specialists in gastrointestinal histopathology</td>
<td>initial diagnosis of high grade (HGD) or severe dysplasia of the gastric epithelium by endoscopic biopsy</td>
<td>reclassified as low grade dysplasia (LGD), HGD, suspicious for invasive carcinoma, or intramucosal carcinoma (IMC) using the Vienna system</td>
<td>high grade/severe dysplasia reclassified pathologist 1 pathologist 2 pathologist 3</td>
<td>18</td>
<td>67</td>
<td>61</td>
<td>33</td>
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<tr>
<td>Vieth (28)</td>
<td>2010</td>
<td>1</td>
<td>738</td>
<td>cases for second opinion</td>
<td>consecutive cases diagnosed as stomach cancer, suspected stomach cancer, suspected neoplasia, adenoma</td>
<td>overall case for second opinion</td>
<td>pseudoneoplastic regeneration Low grade adenoma (41% downgraded, 48% carcinoma) cancer or suspected cancer signet ring cell carcinoma</td>
<td>138</td>
<td>89</td>
<td>49</td>
<td>62</td>
</tr>
<tr>
<td>Nitecki (29)</td>
<td>1995</td>
<td>2</td>
<td>186</td>
<td>one internal and one external pathologist</td>
<td>retrospective review of histological specimens from patients surviving &gt; 3 years</td>
<td>patients with pathologic diagnoses of ductal adenocarcinoma who underwent potentially curative pancreatic resection. Excluded those with palliative surgery, pure intraductal or endocrine pancreatic tumours; cancers arising in bile duct, duodenum, ampulla of Vater</td>
<td>3-year survivors (2nd review) all patients (assumes non-survivors were correctly diagnosed, no 2nd review of these)</td>
<td>31</td>
<td>39</td>
<td>49</td>
<td>62</td>
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<tr>
<td>Conlon (30)</td>
<td>1996</td>
<td>1</td>
<td>131</td>
<td>retrospective review of pathologic material from patients surviving &gt; 5 years</td>
<td>patients with histologically confirmed diagnosis of invasive ductal adenocarcinoma of the pancreas who underwent resection with curative intent</td>
<td>5-year survivors (2nd review) all patients (assumes non-survivors were correctly diagnosed, no 2nd review of these)</td>
<td>25</td>
<td>52</td>
<td>52</td>
<td>10</td>
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<tr>
<td>Lograno (31)</td>
<td>2000</td>
<td>1</td>
<td>36</td>
<td>cytopathologists</td>
<td>slide review of false negative cases, not blinded</td>
<td>pancreatobiliary brushing cytology specimens determined false negative by histology or clinical correlation</td>
<td>false negative due to interpretation false negative due to technical (slide preparation) errors</td>
<td>36</td>
<td>36</td>
<td>83</td>
<td>83</td>
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<td>Author</td>
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<td>Agreement %</td>
<td>Kappa</td>
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<tr>
<td>Luttges (32)</td>
<td>2000</td>
<td>1</td>
<td>70</td>
<td>initial experienced, 2nd in 1st year of training</td>
<td>review of grading and proliferation index (PI)</td>
<td>ductal adenocarcinoma of the head of the pancreas from partial duodenopancreatectomy</td>
<td>tumour grade proliferation index</td>
<td>26</td>
<td>74</td>
<td>0.17 0.52</td>
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<td>Carpelan-Holmstrom (33)</td>
<td>2005</td>
<td>3</td>
<td>24</td>
<td>expertise in pancreatic pathology</td>
<td>slide review, double blinded</td>
<td>cases in registry with pancreatic cancer and &gt; 5 year survival recorded as histologically proven pancreatic ductal adenocarcinoma (PDAC)</td>
<td>PDAC determined wrong on review</td>
<td>24</td>
<td>58</td>
<td>42</td>
<td></td>
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<tr>
<td>Niedergethmann (34)</td>
<td>2008</td>
<td>1</td>
<td>207</td>
<td>pathologist</td>
<td>review to look for unidentified cases of intraductal papillary-mucinous neoplasms (IPMN)</td>
<td>reevaluated pancreatic resections initially diagnosed as cystic or small solid tumours (excluded typical diagnoses such as ductal adenocarcinoma, chronic pancreatitis)</td>
<td>cystic/small tumours reevaluated as IPMN</td>
<td>207</td>
<td>26</td>
<td>74</td>
<td>100</td>
</tr>
<tr>
<td>Pomianowska (35)</td>
<td>2012</td>
<td>2 (consensus)</td>
<td>207</td>
<td>experienced pancreatic pathologists blinded to original diagnosis</td>
<td>Surgery, primary and review pathology at a third-level referral institution</td>
<td>Classification of tumour origin in patients undergoing pancreatectoduodenectomy for periampullary adenocarcinoma</td>
<td>Classification of tumour origin</td>
<td>207</td>
<td>27</td>
<td>73</td>
<td>0.64</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Kulesza (36)</td>
<td>2004</td>
<td>1</td>
<td>64</td>
<td>cytopathologists</td>
<td>independent grading of core needle biopsy samples of hepatocellular carcinoma (HCC)</td>
<td>grades of well differentiated (WD), moderately differentiated (MD), poorly differentiated (PD); also compared to &quot;true&quot; diagnosis determined from excisional biopsy</td>
<td>agreement among cytopathologists</td>
<td>26</td>
<td>22</td>
<td>31 87 0.66</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.32 0.53</td>
</tr>
<tr>
<td>Lind (37)</td>
<td>1995</td>
<td>1</td>
<td>528</td>
<td>pathologists</td>
<td>peer review after 1st pathologist finished report; excluded cases where consensus could not be reached</td>
<td>all diagnostic surgical pathology biopsies; major error=clinically significant; minor=no treatment change</td>
<td>gastrointestinal</td>
<td>528</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Prescott (38)</td>
<td>1995</td>
<td>1</td>
<td>13</td>
<td>review at regional cancer treatment centre</td>
<td>cases with confident 1st diagnosis, excluded cases where 2nd opinion sought</td>
<td>gastrointestinal tract</td>
<td>23</td>
<td>8 15</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kronz (39)</td>
<td>1999</td>
<td>1</td>
<td>1083</td>
<td>mandatory 2nd opinion</td>
<td>all cases referred to treating institution, excludes consult cases with uncertain diagnosis</td>
<td>gastrointestinal tract (4/13 discrepancies non-cancer related)</td>
<td>1</td>
<td>99</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Layfield (40)</td>
<td>2002</td>
<td>1</td>
<td>20</td>
<td>review of outside cytology material</td>
<td>liver</td>
<td>bile duct, liver, pancreas total</td>
<td>11</td>
<td>27</td>
<td>18</td>
<td>9 73</td>
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**Studies that reported on several cancer sites**
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<th>Author</th>
<th>Year</th>
<th># 2nd Reviewers</th>
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<th># Specimens of Subtype</th>
<th>Discrepancy, %</th>
<th>Agreement</th>
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<tr>
<td>Weir [41]</td>
<td>2003</td>
<td>1</td>
<td>191</td>
<td>interinstitutional, at request of clinical staff of treating institution</td>
<td>compared 1st and treating institution reports; major=clinical impact</td>
<td>histological samples: gastrointestinal</td>
<td></td>
<td></td>
<td>182</td>
<td>5</td>
</tr>
<tr>
<td>Ahmed [42]</td>
<td>2004</td>
<td>1</td>
<td>52</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>liver, gall bladder, biliary tract, pancreas, salivary glands</td>
<td></td>
<td></td>
<td>52</td>
<td>33</td>
</tr>
<tr>
<td>Tsung [43]</td>
<td>2004</td>
<td>1</td>
<td>122</td>
<td>pathologists</td>
<td>all surgical pathology cases referred to cancer center for therapy or second opinion</td>
<td>major discrepancies: benign to malignant or vice versa, different type of neoplasm, change in N or M of TNM classification</td>
<td>gastrointestinal tract</td>
<td></td>
<td></td>
<td>105</td>
</tr>
<tr>
<td>Raab [44]</td>
<td>2005</td>
<td>1</td>
<td>2090</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>gastrointestinal and other hepatobiliary</td>
<td></td>
<td></td>
<td>1850</td>
<td>240</td>
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<tr>
<td>Renshaw [45]</td>
<td>2006</td>
<td>1</td>
<td>1143</td>
<td></td>
<td></td>
<td></td>
<td>gastrointestinal, all discrepancies reviewer missed lesion</td>
<td></td>
<td></td>
<td>1143</td>
</tr>
<tr>
<td>Raab [47]</td>
<td>2008</td>
<td>1</td>
<td>87</td>
<td>subspecialists</td>
<td>focused review of specific case types</td>
<td>colon</td>
<td></td>
<td></td>
<td>87</td>
<td>6</td>
</tr>
<tr>
<td>Bomeisl [48]</td>
<td>2009</td>
<td>1</td>
<td>78</td>
<td>Cytopathologist or anatomic pathologist</td>
<td>interinstitutional consultation, FNA, prior to treatment or patient requested 2nd opinion</td>
<td>major or ≥2 step deviation (unsatisfactory, benign, atypical, suspicious, malignant) or change in treatment or prognosis</td>
<td>Liver Pancreas</td>
<td></td>
<td></td>
<td>78</td>
</tr>
<tr>
<td>Lu [49]</td>
<td>2009</td>
<td>1</td>
<td>834</td>
<td>external consultation</td>
<td>digestive system liver, gall pancreas</td>
<td></td>
<td></td>
<td></td>
<td>834</td>
<td>73</td>
</tr>
</tbody>
</table>
B. Gastric Cancer

Four studies reported on pathology review in gastric cancer. The largest study by Vieth et al (28) found a 51% discrepancy in cases diagnosed as stomach cancer, suspected cancer, or suspected neoplasia/adenoma that had been sent for second opinion. The same study (28) found a 28% discrepancy in cases diagnosed as gastric cancer or suspected cancer. While the reason for second opinion could not be determined, the high discrepancy rate may reflect the fact that second opinion is more likely requested in the most difficult cases.

The study by Sarela et al (27) found that dysplasia initially graded as high or severe was reclassified by three pathologists in 44%, 73%, and 81% of samples. Plummer et al (25) reported discrepancy rates of 22% to 42% for precancerous lesions. Vieth et al (28) found 89% of low-grade adenoma had discrepancies, with 41% downgraded and 48% upgraded to carcinoma.

C. Colorectal Cancer

One study (21) reporting on secondary review in colorectal cancer used neoadjuvant therapy and radiation, and, therefore, the results cannot be applied to colorectal cancer generally. Seven studies (12,13,15-19) deal with colorectal polyps. Denis et al (16) tested polyps found after fecal occult blood test screening and estimated 55% discrepancy in histological type or degree of dysplasia, including 27% major and 28% minor. Yoon et al (12) reported a 33% discrepancy in histological type of adenomas and 44% discrepancy in degree of dysplasia. Studies reported 18% discrepancy in the diagnosis of advanced adenomas (13). The reinterpretation of hyperplastic polyps led to a change to sessile serrated adenoma in 6% of samples in one study (19), and changes of 43%, 30%, and 85% by three pathologists in another study (18). While the studies report large discrepancy rates, it should be noted that pathologic diagnosis of serrated adenoma has improved recently due to increased experience with these lesions and changes in classification systems, and thus several of the papers (e.g., (18,19)) are no longer relevant to current practice. Some of the authors indicate there is large variation among gastrointestinal (GI) pathologists, existing morphological criteria are not reproducible, and, therefore, clarification of nomenclature for serrated polyps is required.

The study by Komuta et al (15) reported that 14% of malignant colorectal polyps had the diagnosis changed to carcinoma in situ on review. The study by Denis et al (16) reported 26% of malignant polyps had misclassification with potential impact on the treatment.

D. Anal Cancer

One study on anal dysplasia (14) was located; it found only poor to moderate agreement in grading. Complete concordance on the severity of anal dysplasia among the original and three review pathologists was observed in 32% of cases. They concluded that a better tool for the assessment of dysplasia is required, possibly including a simplified grading system and molecular biology markers.

E. Pancreatic Cancer

A review of false negative pancreatobiliary brushing cytology specimens (31) found 17% false-negative cases were due to pathologic misinterpretation and 17% due to technical errors such as slide preparation. Ductal adenocarcinomas of the head of the pancreas had a 26% discrepancy in histopathological grade between the original and review results (32), though this may be of limited relevance as one of the pathologists was inexperienced (first year of training). Cases recorded in a cancer registry as histologically proven pancreatic ductal adenocarcinoma with > 5 year survival were found to have a wrong diagnosis based on
pathology review in 58% of cases. Samples initially identified as cystic or small tumours were reclassified as intraductal papillary-mucinous neoplasms in 26% of cases (34).

F. Liver Cancer

Kulesza et al (36) reported on the agreement of cytopathologists in grading core needle biopsy (CNB) samples of hepatocellular carcinoma (HCC). Kappa values for agreement were 0.53, 0.32, and 0.66 for poorly, moderately, and well-differentiated HCC, respectively. There was 41% discrepancy in grade between the CNB and excisional biopsies. No studies specifically on liver resection specimens were found in the systematic review. Interinstitutional reviews which included several cancer sites report 6% to 33% discrepancies for liver samples, and major discrepancies of 0.4% to 9%. Tsung et al (43) reported on several types of surgical pathology samples and indicated discrepancy in one out of 17 liver samples (6%). A survey on the impact of review after sign-out by Raab et al (44) included self-reported results from 74 institutions. For hepatobiliary samples, there were discrepancies in 7% of samples, including 0.4% that were judged major.

Clinical Practice Guidelines

The SIGN guideline on the management of esophageal and gastric cancer (51) recommends that diagnoses of invasive malignancies in esophageal or gastric cancer should be reviewed by a specialist GI pathologist at an appropriate multidisciplinary meeting. There is significant inter- and intra-observer variation among Western pathologists in the diagnosis of dysplasia and intramucosal cancer in patients with esophageal and gastric cancer. The revised Vienna classification for reporting dysplasia should be used. Grading is reasonably good for high-grade dysplasia/intramucosal adenocarcinoma and ‘no dysplasia’ but less reliable for grades in between. Low-grade dysplasia is often overdiagnosed by non-specialist pathologists. Where radical intervention is contemplated on the basis of high-grade dysplasia or early adenocarcinoma, the diagnosis should be validated by a second pathologist experienced in this area, and further biopsies should be taken if there is uncertainty. The evaluation of suspected high-grade dysplasia in Barrett’s esophagus biopsies should be undertaken with knowledge of the clinical and endoscopic background, and biopsies should be reviewed at a multidisciplinary meeting with access to the clinical information.

European guidelines (European Union/IARC) for quality assurance in colorectal cancer screening and diagnosis (52) states that variation exists in evaluating high-risk features of pT1 colorectal cancer, and consideration should be given to obtaining an opinion from a second histopathologist if surgical resection is recommended.

The European Society for Medical Oncology (ESMO) Guideline on gastrointestinal stromal tumours (53) recommends expert pathological second opinion in all cases when the original diagnosis is made outside reference centres.

The PEBC/CCO Guideline on Hepatic, Pancreatic, and Biliary Tract (HPB) Surgical Oncology Standards (54) recommends a comprehensive approach to the investigation of HPB patients in specialized centres. Sophisticated technology and diagnostic expertise, especially in imaging and pathology, may not be widely available but is often required to sort out the more difficult cases. There needs to be a specialized liver pathologist onsite. A pathologist with a special interest in HPB diseases and a commitment to developing the appropriate expertise is required.

The International Gastric Cancer Linkage Consortium consensus guideline on hereditary diffuse gastric cancer (HDGC) (55) recommends expert histopathological confirmation of these early lesions. Confirmation by an independent histopathologist with experience in this area is strongly recommended for precursor lesions of early invasive signet ring cell carcinoma (in situ signet ring cell carcinoma, pagetoid spread of signet ring cells
below the preserved epithelium of glands, and foveolae). As experience in the observation of prophylactic gastrectomies for HDGC is quite limited in most pathology departments due to the rarity of these surgical specimens, the guideline recommends centres of excellence be established worldwide, along with a virtual bank of lesions observed in the setting of HDGC. It is essential that clinical experiences and research progress are combined in order to benefit patient management.

The UK/Ireland guideline on gastroenteropancreatic neuroendocrine tumours (NETs) (56) recommends management by a multidisciplinary team (MDT) at a referral centre which includes specialist physicians in NETs (gastroenterologists, oncologists and/or endocrinologists), surgeons, radiologists, nuclear medicine specialists, histopathologists, and clinical nurse specialists. Pathologists dealing with NETs should have a special interest in endocrine or gastrointestinal pathology or participate in a network with the opportunity for pathology review.

DISCUSSION

In some of the studies, missing information was a major reason for secondary review. Specimens with reports that are missing key information such as type, grade, or margins need to be referred back to the primary pathologist or have secondary pathology review. Initial (primary) pathology reports should include synoptic reporting, as stipulated in the CAP protocols (see http://www.cap.org), which are based on the American Joint Commission on Cancer (AJCC) standards (57). CCO and the CAP/APC have endorsed the CAP cancer checklists as the content standard for pathology reporting (58,59). Synoptic reporting can help ensure that reports are complete, and in Ontario such reports are currently required for resection specimens (esophagus, gallbladder, hepatocellular carcinoma, intrahepatic bile ducts, pancreas, perihilar bile ducts, small intestine and ampulla neuroendocrine tumours, small intestine, stomach) (59).

Most studies base dealt with primary review by pathologists without specific expertise in gastrointestinal cancer, followed by secondary pathology review by a specialist prior to treatment, or retrospective evaluation to verify the diagnosis or specific features. There is only limited information on secondary review when the primary pathologist is a gastrointestinal pathologist, and this should continue to be decided on a case-by-case basis or institutional policy. The authors believe that secondary review, when conducted, should be by a gastrointestinal pathologist; however, the evidence extracted did not directly address this issue. In Canada there is no precise definition of a gastrointestinal pathologist. In Ontario most secondary review will be in cancer centres where pathology specialization occurs.

A. Barrett’s Esophagus

The SIGN guideline (51) recommends secondary pathology review whenever radical intervention is contemplated based on high-grade dysplasia or early adenocarcinoma. Current practice in Ontario is to review biopsies prior to surgery, and the studies in Table 1 support review of high-grade dysplasia. For low-grade dysplasia specimens there is considerable variability between pathologists and in different practices. While under-diagnosis is an issue, the value of routine secondary review is questionable. Most patients will receive follow-up and thus further diagnosis at a later date; whether or not follow-up is planned may be a consideration in deciding on secondary pathology review.

B. Gastric Cancer

The SIGN guideline (51) recommends secondary pathology review whenever radical intervention is contemplated based on high-grade dysplasia or early adenocarcinoma. In
Ontario, HER2 testing is currently mandated for gastric and gastroesophageal junction adenocarcinomas (60) (letters from Jennifer Hart, Manager, Pathology & Laboratory Medicine Program, Cancer Care Ontario: “Gastric HER2/Neu testing FAQ’s - final” 2011 Nov; “Gastric HER2/Neu testing update” 2012 Dec 19). CCO guidelines indicate that these should be sent at the time of the first diagnosis. Through the course of this testing, the gastrointestinal pathologist is performing a limited review in order to do the HER2 testing; this is predominantly in the areas of tumour type (intestinal versus diffuse) and grade. An inability to assess the HER2 status due to uncertainty regarding the diagnosis of gastric cancer would be part of the pathology report.

The authors consider high-grade dysplasia in the stomach as fairly rare and, therefore, there is a high level of suspicion that warrants confirmation by a secondary pathology review. There was a very high discrepancy rate for low-grade gastric dysplasia, though most cases will receive follow-up and rebiopsy.

C. Colorectal Cancer

Most of the studies reported on colorectal polyps, generally detected on colonoscopy or screening studies. Guidelines on the classification and reporting of colorectal polyps such as those recently developed by the Pan-Canadian Consensus Group should be followed (61,62). The experience of the authors is that a diagnosis of colorectal cancer is usually straightforward, with few discrepancies, and does not warrant routine secondary review for specimens diagnosed as colorectal cancers or non-malignant colorectal polyps. Secondary pathology review should be considered for malignant polyps (adenomas containing early invasive adenocarcinomas) as these had misclassification with potential treatment impact. For malignant polyps, specific factors such as margin, stage, grade, lymphovascular space invasion, and budding as well as possible overcalling of misplaced epithelium are important and may be influenced by technical issues during sample processing.

Several studies have reported high interobserver variation among pathologists assessing dysplasia in ulcerative colitis (a subtype of IBD) (63-66). No studies of flat dysplasia in IBD were included in the evidence base. The authors’ experience is that flat dysplasia is difficult to diagnose and has the potential for mistreatment. Both low- and high-grade flat dysplasia are significantly correlated with concurrent invasive carcinoma, and the diagnosis will lead to the potential consideration of colectomy. Current practice in Ontario is to have a gastrointestinal pathologist review specimens with evidence of flat dysplasia.

D. Anal Cancer

The only study found concluded a better tool for assessment of dysplasia may be required.

E. Pancreas and Ampulla of Vater

Most of the studies in the evidence review dealt with resected specimens but are of limited relevance due to the age of the studies (i.e., not using current methodology) and/or specific subgroups studied. The PEBC/CCO document Hepatic, Pancreatic, and Biliary Tract (HPB) Surgical Oncology Standards (54) as implemented in Ontario (67) recommends that all pancreatic surgery should be done at a specialized centre with multidisciplinary care including a pathologist with special interest and expertise in HPB diseases. The experience of the authors is that diagnosis of ampullary cancer is very difficult, and many pathologists are unfamiliar with this disease. A correct diagnosis is important as it will determine whether or not surgery is required.

Some gastrointestinal pathologists are less experienced than cytologists in diagnosing uncommon cytology samples, and, therefore, ampullary and periampullary cytology or brush
cytology specimens should be reviewed by a cytopathologist or gastrointestinal pathologist familiar with these lesions. Biopsies are usually for diagnosis or treatment planning for unresectable cancer, and current practice in Ontario is that biopsy and pathology review are to be performed at an HPB Cancer Centre.

F. Liver Cancer
The authors consider HCC to be a very difficult diagnosis that warrants review by a specialist. This recommendation is consistent with the PEBC/CCO document Hepatic, Pancreatic, and Biliary Tract (HPB) Surgical Oncology Standards (54), as implemented in Ontario (67), which recommends that all specimens should be viewed by a pathologist with a special interest in HPB diseases and a commitment to developing the appropriate expertise.

It is the experience of the authors that biopsies in cases with a liver mass have a higher likelihood of being cancer. Such biopsies, if initially reviewed by a pathologist in the community, should have secondary review by a gastrointestinal pathologist at a HPB centre.

G. Gastrointestinal Stromal Tumours (GIST) and Neuroendocrine Tumours (NET)

No studies on secondary pathology review in GIST or NET specimens were found in the evidence review. ESMO (53) recommends an expert pathological second opinion in all cases of GIST when the original diagnosis is made outside reference centres. A consensus guideline (56) by members of the UK and Ireland Neuroendocrine Tumour Society (endorsed by the British Society of Gastroenterology, the Society for Endocrinology, the Association of Surgeons of Great Britain and Ireland, the British Society of Gastrointestinal and Abdominal Radiology) recommends that pathologists dealing with NETs should have a special interest in endocrine or gastrointestinal pathology, or participate in a network with the opportunity for pathology review; the management of patients should be decided by multidisciplinary teams.

H. Appendiceal Mucinous Tumours
This continues to be one of the “problem areas” in gastrointestinal pathology, mostly due to the controversies existing around the tumour classification and nomenclature. Since this is an evolving area of practice, the current literature does not have evidence to support specific recommendations for secondary review. At this time, the authors see greater value for pathologists to stay current in their knowledge regarding these issues and to establish clear communication with the radiologists and surgeons within their own institutions.

CONCLUSIONS
A. Barrett’s Esophagus
Specimens with diagnosis of high-grade dysplasia in Barrett’s Esophagus had a high rate of clinically relevant discrepancy and, therefore, warrant secondary review. There were high discrepancy rates for low-grade dysplasia, though most patients will receive follow-up and thus further diagnosis at a later date.

B. Gastric Cancer
Gastric cancers should have secondary pathology review prior to treatment. In Ontario this review many occur during HER2 testing. The authors consider high-grade dysplasia in the stomach as fairly rare, and, therefore, there is a high level of suspicion that warrants confirmation by secondary pathology review. There was a very high discrepancy rate for low-grade gastric dysplasia, though most cases will receive follow-up and rebiopsy.

C. Colorectal
Routine secondary pathology review is not required for specimens diagnosed as colorectal cancers or non-malignant colorectal polyps. Secondary pathology review should be considered for malignant polyps (adenomas containing early invasive adenocarcinomas). A gastrointestinal pathologist should review specimens with evidence of flat dysplasia in IBD patients.

D. **Anal Cancer**
   As evidence is extremely limited (one study) no conclusions are made.

E. **Pancreas and Ampulla of Vater**
   Pancreatic resection specimens should be reviewed by a pathologist with special interest and expertise in HPB disease. Ampullary and periampullary cytology or brush cytology specimens should be reviewed by a cytopathologist or gastrointestinal pathologist familiar with these lesions. Biopsy specimens should be reviewed by a gastrointestinal pathologist.

F. **Liver Cancer**
   Liver biopsies in cases with a liver mass and all liver resection specimens should be reviewed by a pathologist with special interest and expertise in HPB disease.

G. **Gastrointestinal Stromal Tumours (GIST) and Neuroendocrine Tumours (NET)**
   As mandated by CCO in Ontario, the minimum data set of the synoptic report and all diagnostic parameters for gastrointestinal stromal tumors and neuroendocrine tumours need to be reported. If the local laboratory cannot meet these requirements then specimens should be sent to a laboratory with expertise in these tumour types. Other guidelines recommend that pathologists dealing with NETs should have a special interest in endocrine or gastrointestinal pathology.

H. **Appendiceal Mucinous Tumours**
   Controversies exist around classification and nomenclature of appendiceal mucinous tumours. Pathologists need to stay current in their knowledge and establish clear communication with the radiologists and surgeons within their own institutions.

**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.

**CONFLICT OF INTEREST**
In accordance with the PEBC Conflict of Interest (COI) Policy, the authors were asked to disclose potential conflicts of interest. For the Working Group potential conflicts of interest 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

The Pathology & Medicine Program and the Working Group would like to thank the following individuals for their assistance in developing this report:

- Dr. John Srigley, Dr. Sandy Boag, Glenn Fletcher, Dr. Suhas Joshi, Dr. Mahmoud Khalifa, and Dr. Brendan Mullen for taking the lead in the overall pathology secondary review project.
- Melissa Brouwers, Roxanne Cosby, Sheila McNair, Hans Messersmith, and Leslie Souter, for providing feedback on draft versions.
- Denise Kam for providing research assistance and for managing communication among the working group and with the reviewers.
- Julia Shen for conducting a data audit.
- Carol De Vito for copyediting.
- Jennifer Hart and Dana Wilson-Li of Cancer Care Ontario.

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

Funding
The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

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CS reported consulting fees and grants from Hollman-LaRoche to validate HER2 testing in gastroesophageal/gastric adenocarcinomas and create an information document.
Appendix II. Reproducibility studies (data not extracted).

Gastrointestinal (1-17)


**Colorectal (18-41)**


Esophagus (42-54)


Liver, Bile, Pancreas (55-68)


