Will Computer-Aided Detection and Diagnosis Revolutionize Colonoscopy?

Colorectal cancer (CRC) remains a critical health concern and a significant financial burden, not only in North America, but worldwide. This highlights the importance of colonoscopy as a cost-effective means of preventing CRC through the identification and removal of polyps.[1] However, colonoscopy is operator dependent. Variability in the skill and diligence of the endoscopist to detect and remove polyps impacts the ability of colonoscopy to reduce the risk of interval CRC and its associated mortality.[2] Moreover, the use of colonoscopy itself carries its own economic footprint, specifically, the associated costs of removing and histologically evaluating all identified polyps regardless of their malignant potential.[3] With the above point in mind, efforts have been made to improve the adenoma detection rate (ADR) through various strategies, including the use of high-definition endoscopes and cap attachments.[4] Furthermore, enhanced imaging modalities have been developed as a means of performing an "optical biopsy," thereby empowering the endoscopist to resect and discard diminutive adenomas without pathology review or to leave diminutive distal hyperplastic polyps in situ. Unfortunately, these interventions have their limitations, specifically outside the hands of expert endoscopists.[5] Therefore, a need exists for further technical advancements to optimize both the detection of polyps and their endoscopic evaluation.

Computer-aided detection (CADe) and computer-aided diagnosis (CADx) are systems that incorporate a computer's ability to learn and perform specific tasks. Through advances in machine learning and deep learning methodology, computers can now learn and perform specific endoscopic tasks that previously were the responsibility of the endoscopist. Although still in their infancy, CADe and CADx have the potential to revolutionize endoscopy. This article's focus is to provide an overview of the use of CADe and CADx in colonoscopy, focusing on 3 key areas: (1) adequacy of mucosal inspection, (2) polyp detection, and (3) optical biopsy.

Adequacy of Inspection Technique

Careful inspection of the colonic mucosa is the cornerstone of a quality colonoscopy. A surrogate marker for this is the ADR, defined as the percentage of patients with $\geq$1 adenoma identified on screening colonoscopy. ADR has been embraced as the pivotal colonoscopy quality metric by the quality task force of the American College of Gastroenterology/American Society for Gastrointestinal Endoscopy, with an ADR target for asymptomatic average-risk adults undergoing screening colonoscopy of $\geq$25% (men, $\geq$30%; women, $\geq$20%).[6] The usefulness of ADR was validated by Corley et al,[2] who found a 3% reduction in the risk of interval CRC and a 5% reduction in interval CRC-related mortality for every 1% increase in the ADR. The ADR can be improved by using high-definition colonoscopes, split-dose bowel preparations, nondevice techniques such as optimized inspection technique, and tools to improve mucosal exposure and highlight flat lesions.[4] However, the highest ADRs reported have been achieved by endoscopists using only split-dose preparations, high-definition colonoscopes, and optimal technique.[7] ADR and its variants such as adenomas per colonoscopy provide only a post-procedure assessment of performance quality that may lead to steps to improve performance in future examinations. Until recently, an automated means of assessing and correcting colonic mucosal inspection in real time has been unavailable.

The EM-Automated-RT (EndoMetric Inc, Ames, IA)[8,9] is a computer system that allows for real-time analysis and feedback for mucosal inspection during colonoscopy. It does so through 3 mechanisms: (1) differentiating informative and noninformative (blurry) frames, (2) detecting and quantifying residual stool/debris, and (3) measuring the effort to inspect all colonic mucosa. The latter is achieved by dividing the endoscopic view into quadrants (Supplemental Figure 1). During withdrawal, when the colonic lumen is seen in a particular quadrant, the opposing quadrant of colonic mucosa is marked as inspected. When each quadrant has been sequentially inspected, the EM-Automated-RT provides the endoscopist with an increase in their inspection score. This technology was recently evaluated in a prospective study among 10 third-year gastroenterology trainees performing 483 colonoscopies.[9] The trainees were randomly assigned to use the EM-Automated RT. Subsequently, the de-identified endoscopic videos were evaluated by 2 blinded investigators. The results showed that the EM-Automated-RT leads to a significant increase in the mean mucosal visualization score, the mean debris removal score, the mean bowel distension score, and the mean withdrawal time (all $P < .02$). Although further studies are needed to evaluate this software as a means of assessing and affecting colonoscopy quality among practicing endoscopists, it seems to be a promising tool for objective real-time quality assessment.

Polyp Identification

Even with diligent exposure of the colonic mucosa, polyps may not be detected because of their small or flat morphology, or minimal color differences between the polyp and normal mucosa. The relative contributions of failed mucosal exposure and failed recognition of exposed polyps are uncertain. However, the contributions of high definition[10] and chromoendoscopy[11] to detection and the recent demonstrations that brighter forms of electronic chromoendoscopy improve detection are clear evidence that

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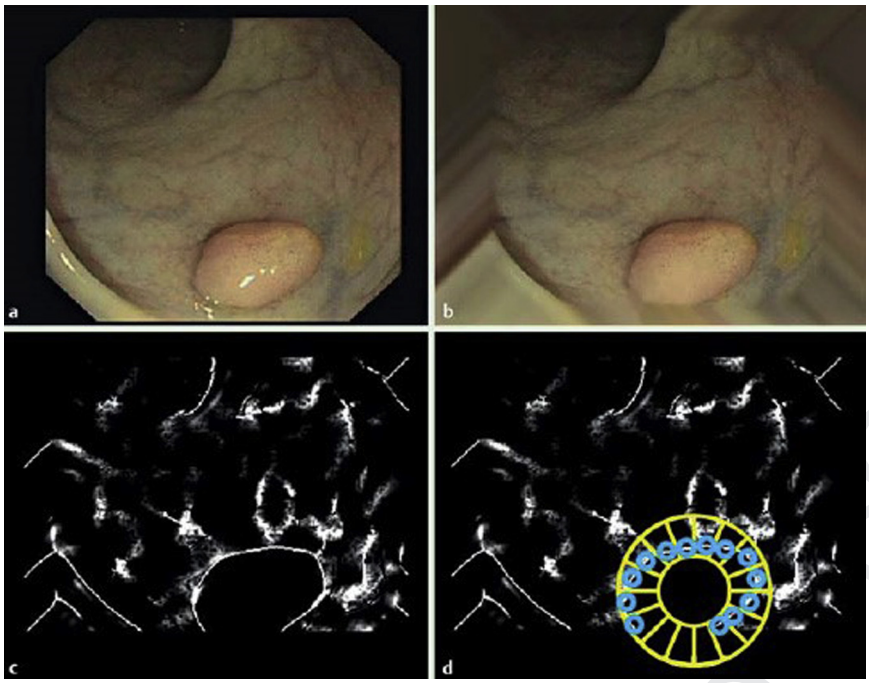

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Figure 1. Computer-aided polyp detection. (Reprinted from Fernandez-Esparrach G et al,[14] Exploring the clinical potential of an automatic colonic polyp detection method based on the creation of energy maps. Endoscopy 2016;48:837-842. Copyright © 2016 with permission from Thieme Medical Publishers Inc).

failure to recognize exposed lesions is a significant contributor to missed lesions. In a 2006 systematic review and meta-analysis, 6 tandem colonoscopy studies showed a pooled miss rate of 22% for all polyps.[12] This varied by adenoma size with pooled miss rates of 2.1% for adenomas ≥10 mm, 13% for adenomas 5-10 mm, and 26% for adenomas 1-5 mm. This finding highlights that, regardless of expertise, polyps can be difficult to identify. Therefore, automating the detection of CRC and precancerous lesions through incorporation of CADe carries the potential to improve patient outcomes and resource use.

CADe for polyps has been evaluated by several groups in the field of virtual colonoscopy over the last decade, but there has been, until recently, less effort in optical colonoscopy. The first computer-based system for polyp detection, described by Karkanis et al,[13] used color and texture analysis of the colonic mucosa to identify polyps. Using a set of 180 images derived from 60 colonoscopy videos containing adenomas, their detection system was able to identify polyps with 90% sensitivity and 97% specificity. Because this system is based on evaluation of static images, its usefulness during endoscopy is limited.

New CADe systems[14,15] have emerged (Figure 1). The Polyp-Alert system (EndoMetric Inc, Ames, IA),[15] described by Wang et al in 2015, uses detection of polyp edges to highlight exposed polyps during colonoscopy videos. The technique analyzes every third video frame, approaching real-time analysis. Sixty-one complete colonoscopy videos were randomly selected for the study; 8 were used for training and 53 for testing the Polyp-Alert system. The Polyp-Alert system correctly detected 98% of polyps, although it averaged 36 false-positive detections per colonoscopy. False positives commonly resulted from protruding folds, the appendiceal orifice, the ileocecal valve, and areas with residual fluid. Several of these causes of false positives should be easily dismissed by experienced colonoscopists. Thus, near real-time CADe systems for polyp detection hold great promise for improving polyp detection and reducing operator dependence during colonoscopy.

Optical Biopsy

Optical biopsy refers to endoscopically predicting histology through the use of advanced imaging modalities alongside validated classification systems (eg, narrow-band imaging [NBI] international colorectal endoscopic [NICE] classification).[16] A specific paradigm of interest is the diagnosis and differentiation of diminutive precancerous adenomas and diminutive non-neoplastic hyperplastic polyps. This is in part driven by the low likelihood of either invasive cancer or advanced histology among polyps ≤5 mm.[17] Two strategies have emerged: (1) the "resect and discard" strategy of removing optically diagnosed diminutive adenomas without sending them for pathology review, and (2) the "diagnose and leave" strategy of optically diagnosing diminutive rectosigmoid hyperplastic polyps and leaving them in situ without sampling.[18] Implementing the former strategy has been estimated to save upwards of US$1 billion in upfront costs.[3] The American Society for Gastrointestinal Endoscopy produced the Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) guidelines recommending: (1) ≥90% agreement for post-polypectomy surveillance intervals for the "resect and discard" strategy, and (2) ≥90% negative predictive value (NPV) for adenomatous histology for the "diagnose and leave" strategy.[18] Unfortunately, optical biopsy is also operator dependent, with a recent systematic review and meta-analysis highlighting the correlation between operator expertise and the ability to meet the PIVI benchmarks for performance.[5] Fortunately, CADx, or for this purpose automated optical biopsy, has the potential to allow even nonexperts to effectively use optical biopsy in the management of diminutive polyps. Four imaging modalities that have effectively assimilated automated optical biopsy are (1) magnifying NBI,[19] (2) endocytoscopy,[20] (3) laser-induced fluorescence spectroscopy,[21] and, more recently, (4) nonmagnification NBI.[22]

Magnifying NBI is the combination of NBI with high-definition magnifying endoscopes, allowing for up to 80× magnifying power. Its role in automated optical biopsy was recently evaluated among 118 colorectal lesions,[19] with histology as the gold standard reference. Lesions were differentiated by

the computer system using the Hiroshima classification into non-neoplastic (ie, hyperplastic) and neoplastic (ie, adenoma or adenocarcinoma with intramucosal invasion). Accuracy, with reference to histology, reached 93% (sensitivity 93%, specificity 93%, positive predictive value [PPV] 93%, NPV 93%). Moreover, there was 93% concordance for subsequent surveillance colonoscopy intervals, therefore meeting both PIVI performance benchmarks.[18]

Endocytoscopy is a method of contact microscopy which allows for cellular, structural, and vessel atypia evaluation in vivo.[20] The EndoBRAIN (Cybernet System Co., Tokyo, Japan), which is a combination of endocytoscopy and NBI, is a platform for automated optical biopsy (Supplemental Figure 2). Captured images by the endoscopist during real-time endoscopy are subsequently analyzed by the EndoBRAIN, which then provides an optical biopsy interpretation within 0.3 seconds. It was recently evaluated on 100 randomly selected images of colorectal lesions that were endoscopically removed and underwent pathology review.[20] The accuracy of the EndoBRAIN was 90% (sensitivity 85%, specificity 98%, PPV 98%, NPV 82%).

Using laser-induced autofluorescence spectroscopy, WavSTAT4 (Pentax Medical., Tokyo, Japan) performs real time, in vivo, automated optical biopsy of colon polyps.[21] This is through an optical fiber that is incorporated into standard biopsy forceps and is triggered upon contact. In a prospective observational study of 27 patients (137 polyps), the accuracy of the WavSTAT4 was 85% (sensitivity 82%, specificity 85%, PPV 51%, NPV 96%).[21] Upon stratified analysis for only diminutive distal polyps, the NPV increased to 100%. Concordance between the WavSTAT4 and histology-driven recommendations for interval colonoscopy reached 89%.

Deep Learning

Until recently, CADe and CADx in endoscopy have been largely dependent on traditional machine learning methodology, whereby the programmer essentially "teaches" the computer which features to focus on; the so-called human feature extraction. However, the emergence of deep learning methodology allows for departure from human perceptual limitations. Deep learning methodology, specifically through the use of deep convolutional neural networks, allows for the use of raw and unprocessed videos,[23] thus, allowing artificial intelligence to be integrated during live endoscopy.

In an attempt to address historical limitations of automated polyp detection, specifically the notable variability in polyp appearance and the lack thereof between polyps and potential mimics (eg, prominent colonic folds, residual debris), Yu et al[24] recently unveiled a CADe platform incorporating a 3-dimensional, fully convolutional network. Their platform was evaluated using the ASU-Mayo Clinic Polyp Database,[25] which contains 20 colonoscopy videos. Precision (P) [true positive/(true positive + false positive)], Recall (R) [true positive/(true positive + false negative)], F1 [2PR/(P + R)], and F2 [5PR/(4P + R)] were used for evaluation with the following results of 88%, 71%, 79%, and 74%, respectively.

To our knowledge, we recently were the first to describe the use of deep learning methodology for automated optical biopsy.[22] Using raw and unaltered NBI video recordings of colorectal polyps, we trained, validated, and subsequently tested our system's ability to differentiate adenomas from hyperplastic polyps using the NICE classification system.[16] These videos were captured with standard colonoscopes (Olympus 190 Series; Olympus America, Center Valley, PA). In real time, the system calculates a credibility score based on fluctuations in the system's NICE classification prediction over successive video frames, after which a final polyp classification is provided within approximately 50 ms alongside an associated probability for the correct diagnosis (Figure 2). Ultimately, 125 diminutive polyp videos were used to test the model after training and validation were completed. The credibility score did not reach $\geq$50% for 19 polyps, which were subsequently excluded from analysis. Of the remaining 106 polyp videos, the overall accuracy, with reference to histology, was 94% (sensitivity 98%, specificity 83%, PPV 97%, NPV 90%). Our alignment with the PIVI benchmarks using non-magnification colonoscopy further reinforces the importance of our findings, which mark a step toward incorporating automated optical biopsy into everyday colonoscopy.

Future Directions

CADe and CADx are rapidly growing disciplines and have many potential applications in healthcare, including imaging, robotic surgery, and genomics. Pertaining to endoscopy, we have reviewed their potentials in colonoscopy and colonic polyps, but it is almost certain that CADe and CADx will have growing roles in other endoscopic domains; this includes the assessment of mucosal healing and dysplasia surveillance in inflammatory bowel disease, dysplasia surveillance in Barrett's esophagus, and the evaluation of pancreatic cystic neoplasms during endoscopic ultrasound, to name a few. "Transfer learning," whereby knowledge gained in one area can be applied to a different but related problem, means the work done to date in the field of endoscopy can help to accelerate future improvements and new applications in other areas. A recent review by the European Society of Gastrointestinal Endoscopy[26] comments on "decision support tools and computer-aided diagnosis," and questions how such systems will be deployed; suggesting the most likely scenario being as a "second reader" with more work needed to have true "stand alone" CADe and CADx systems. We agree with this statement, but only at this precise moment in time, because evidence is lagging behind the technology in this space. We are likely to see rapid advances in the sophistication of CADe and CADx systems in medicine in the near future, and application of artificial intelligence in many representations.

Although the emergence of CADe and CADx technologies are promising, they do have limitations. First, to empower CADe and CADx platforms, large datasets or "big data" are needed,

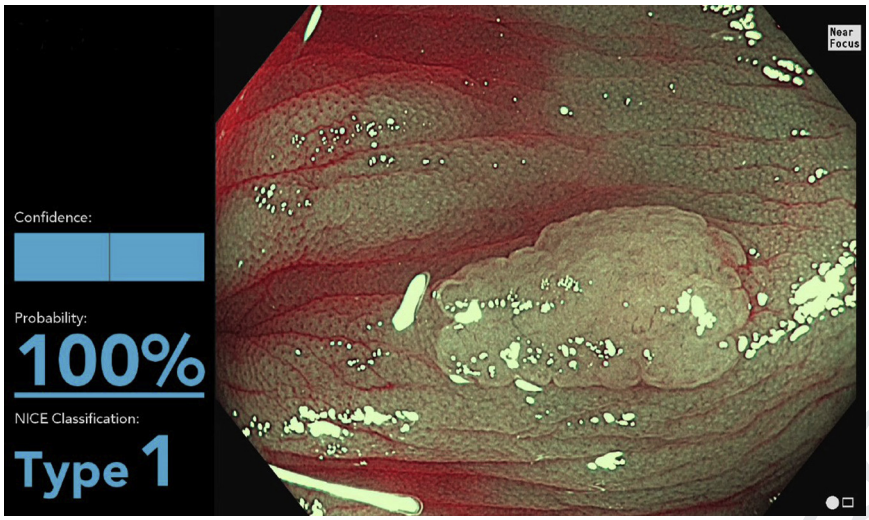

Figure 2. Computer-aided optical biopsy, using deep learning methodology.

especially for those platforms using deep learning methodology. Moreover, with future platforms more likely to incorporate deep learning methodology, more powerful computers will be needed to support them, potentially limiting their ability to be readily incorporated in a standard endoscopy tower. It is also important to note that although magnifying NBI, endocytoscopy, and laser-induced autofluorescence spectroscopy show promise, there is a lack of worldwide availability and expertise for these modalities. Last, a key obstacle that CADe will need to tackle is the detection of flat lesions, with evidence currently limited in this area.

Mori et al[27] have described a "roadmap" to facilitate the assimilation of CADe and CADx into everyday colonoscopy. This includes (1) product development and feasibility studies, (2) clinical trials, (3) regulatory approval, and (4) insurance reimbursement. To start, continued methodological development by incorporating deep learning strategies is needed in the areas of mucosal exposure, lesion highlighting, and optical biopsy. Alongside this, expansion into less explored areas such as submucosal invasion assessment and residual polyp detection are essential. This will naturally feed into further feasibility studies, and, as the technology continues to develop, lead to clinical trials. Of course, controlled trials are needed to assess the ability of computer-aided mucosal inspection and polyp detection strategies to improve ADR, and to assess the performance of automated optical biopsy. This should be coupled with cost-effectiveness analyses across all areas of interest, especially as real-world data begin to emerge. Regarding regulatory approval, WavSTAT4 has already obtained regulatory approval in both the United States and Europe, which will hopefully open the door for other platforms. Last, incentives to accelerate the adoption of CADe and CADx may be necessary, something that is currently being considered by leading countries in this area.

Conclusion

It is now too conservative to suggest that CADe and CADx carry the potential to revolutionize colonoscopy. The artificial intelligence revolution has already begun.

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2017.10.026.

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Conflicts of interest

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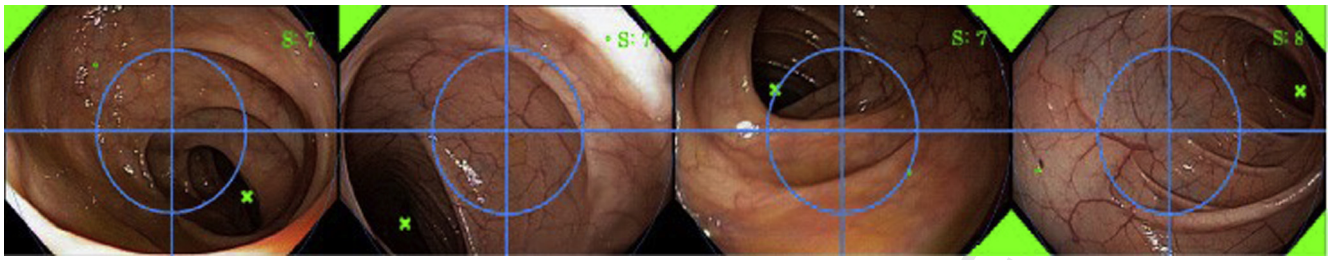

Supplemental Figure 1. Computer-aided colonic inspection. (Reprinted with permission from Stanek SR et al,[8]).

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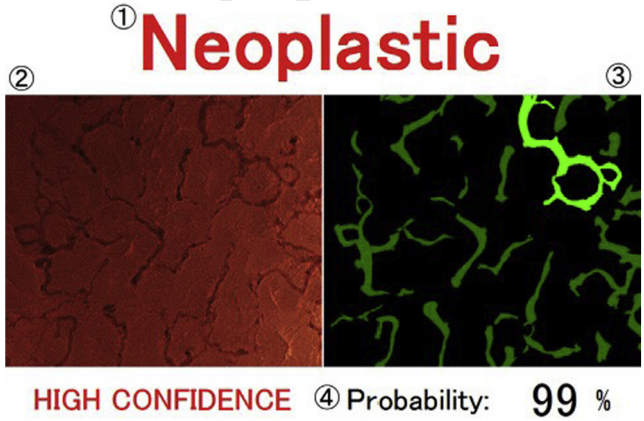

Supplemental Figure 2. Computer-aided optical biopsy. (Reprinted with permissionfrom Misawa M et al,[20]).