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# High-resolution microendoscopy in differentiating neoplastic from non-neoplastic colorectal polyps

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## ABSTRACT

Colorectal cancer is one of the leading causes of death worldwide. The progression from adenoma to cancer is a well known phenomenon. Current clinical practice favors colonoscopy as the preferred modality for colorectal cancer screening. Many novel endoscopic technologies are emerging for the purposes of performing "optical biopsy" to allow real-time histologic diagnosis of polyps. High resolution microendoscopy is a low-cost endoscopic technology that has demonstrated high sensitivity and specificity in differentiating neoplastic and non-neoplastic polyps. With the ability to make real-time conclusions based on the endoscopic appearance of polyps, it is becoming increasingly possible to decrease the rate of unnecessary polypectomies and utilize a "resect and discard" strategy to decrease costs of pathology evaluation. Future directions for this technology include surveillance of

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premalignant conditions such as inflammatory bowel disease. Moreover, the low cost and relative ease of use of this technology lends itself to widespread applicability.

## Introduction

Colorectal cancer (CRC) remains one of the leading causes of death in the world. It is the third most commonly diagnosed cancer in males, and the second in females, with over 1.2 million new cases and 608,700 deaths estimated per year worldwide [1]. The lifetime incidence of CRC in average risk patients is 4.7% in women and 5.0% in men, with 90% of these cases occurring after age 50 [2]. In the United States, CRC is the third leading cause of cancer related death, accounting for about 8% of cancer deaths overall [3]. Patient outcomes are correlated with the stage of the disease at diagnosis. The 5-year survival rate for local disease is about 75%; however, if a patient is found to have distant metastases, the 5-year survival rate drops to 6% [4]. Thus, early detection of CRC, and immediate intervention and management is extremely important.

The US Preventative Services Task Force (USPSTF) has a Grade-A level recommendation for CRC screening: using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults beginning at age 50 years and continuing until age 75 years [5] with the goal of early detection and removal of premalignant adenomas and localized cancer. Colonoscopies have become increasingly favored for CRC screening, with the American College of Gastroenterology considering colonoscopy to be the "preferred" screening test when available [6]. Colonoscopy allows the endoscopist to directly visualize colonic mucosa and subsequently biopsy or excise polyps and local cancers during the same procedure. In addition, colonoscopy is able to detect proximal lesions that would be missed by the screening sigmoidoscopy [7]. Colonoscopy, in conjunction with biopsy and pathological confirmation, remains the current gold standard for the diagnosis of CRC and neoplastic lesions.

Unfortunately, there are some limitations to colonoscopy. Though generally excellent, colonoscopy is not perfect at detecting premalignant or even malignant lesions. One report found that the colonoscopic miss rate, as determined by two same-day endoscopic examinations in 183 patients, was 27% for adenomas <5 mm, 13% for those 6–9 mm, and 6% for adenomas >1 cm [8]. Factors that may contribute to the miss rates include quality of the patient's bowel prep, the training and experience of the endoscopist, the degree of fatigue of the endoscopist, and the amount of time taken by the endoscopist during withdrawal of the colonoscope [9]. Interval or missed cancer rates have been linked inversely to adenoma detection rates [10]. Additionally, flat or depressed lesions, which may also be adenomatous, can be easily missed by colonoscopy, as they are not apparent on conventional white-light endoscopy, and are only recognizable by subtle distortion of the mucosal pattern or by special stains [11]. This is especially important since large flat adenomas may be more likely to contain dysplastic changes or cancer than their polypoid counterparts [12,13].

The vast majority of colorectal polyps may be either adenomatous or hyperplastic in nature. Hyperplastic polyps do not have malignant potential, and most CRC cases arise from adenomas, many of which progress from small to large (>1 cm) polyps, and then to dysplasia and cancer. Currently, there is no completely reliable way to distinguish between benign and non-benign polyps by gross appearance, without the use of advanced imaging modalities; thus, benign polyps are often removed for pathological analysis, leading to unnecessary costs and risk of harm to the patient. These include bleeding, sampling error, and crushed or mishandled specimens. Additionally, more uncommon, but potentially serious, issues can arise such as perforation, biopsy-induced epithelial misplacement into the muscularis propria leading to metastasis [14,15] and post biopsy local fibrosis with subsequent development of the non-lifting sign [16], the latter of which becomes a contraindication for endoscopic mucosal resection. Significant bleeding is possible either at the time of the polypectomy, or several days after, with delayed bleeding occurring in up to 2% of patients who have polyps removed [17]. In severe cases, management of delayed procedural bleeding may require surgery [18]. All of these

limitations accentuate the necessity for reliable advanced imaging that can assist an endoscopist in accurately and precisely identifying abnormal areas in real-time.

## Evolving approaches

Multiple imaging modalities have been proposed and explored in an effort to improve the accuracy and diagnostic yield of endoscopic procedures for identifying neoplastic and pre-neoplastic lesions and therefore allow for a more selective biopsy approach. These include wide-field imaging modalities which are designed to survey large areas of tissue, such as narrow band imaging (NBI), dye-based chromoendoscopy, and autofluorescence imaging (AFI); as well as high-resolution imaging, such as optical coherence tomography (OCT), confocal laser endomicroscopy (CLE), endocystoscopy (ECS), and high-resolution microendoscopy (HRME).

At the same time, there have also been proposals for new endoscopic biopsy strategies. One such approach has been the "resect and discard" strategy. This strategy proposes the discarding of small and diminutive polyps after resection and avoiding the expense of pathological examination [19,20]. Its main assumption is that if endoscopic procedures are able to provide in vivo prediction of polyp histology, the additional value of pathological examination could be limited and as such, subsequent examination would then by inefficient and/or cost-ineffective [21–23]. The American Society of Gastrointestinal Endoscopy (ASGE) has developed the Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) statement to assist in the development of guidelines for colonoscopic management of diminutive (≤5 mm in size) colorectal polyps that may reduce costs and improve patient safety. According to this statement, in order for colorectal polyps of ≤5 mm in size to be resected and discarded, there should be a ≥90% agreement in determining post-polypectomy surveillance intervals between the assessments derived from the optical biopsy of diminutive polyps paired with histo-pathologic assessment of all other polyps >5 mm, compared to decisions based on pathology assessment of all identified polyps. Additionally, the technology should provide a NPV ≥90% for detecting adenomatous histology in diminutive polyps, in order to not resect [24,25].

Much of the initial data and analyses regarding novel endoscopic technologies have been conducted while looking at NBI, and other related forms of electronic chromoendoscopy, such as Fuji intelligent color enhancement [FICE] and i-SCAN [19]. These technologies primarily exploit the neo-angiogenesis of neoplastic lesions in order to differentiate between adenomatous and hyperplastic lesions, by means of light filtering that is applied pre- or post-processing [26–28]. Although tertiary centers have demonstrated high accuracy of electronic chromoendoscopic procedures for in vivo prediction of polyp histology [20,29–31], community-based studies have reported suboptimal results for sensitivity and specificity, only 25% of gastroenterologists assessed polyps with ≥90% accuracy [32,33]. Suboptimal specificity would result in unnecessary surveillance examinations for those with false-positive findings (i. e., with only hyperplastic lesions), limiting the potential economic advantage of the resect and discard strategy. Conversely, low sensitivity results in surveillance not being offered to some in whom it may actually be appropriate, risking interval cancer.

## High-resolution imaging/HRME device

High-resolution imaging modalities are those which can provide imaging at subcellular resolution. These approaches, which can provide "optical biopsy" images, similar to those seen in histology, also have the advantage of being available in real time. High-resolution imaging is especially useful for targeting biopsies by providing a live image of the cellular architecture before the biopsy is taken, though several other uses have been proposed. Several different high-resolution imaging modalities are used in vivo; these include CLE and HRME, though a single in-vivo pilot study looking at ECS in the colon has recently been published [34].

CLE is a powerful diagnostic and surveillance tool, thought to achieve the highest sensitivity and specificity of any high-resolution modality to date. In general, the reported results have been substantial, with accuracy rates often greater than 90% [35–41]. And while CLE platforms have been the most promising as complementary tools to white-light colonoscopy with extremely high sensitivity

and specificity, their widespread use has been limited by their high cost, need for intravenous contrast, and relatively high learning curve [42].

The high-resolution microendoscope (HRME) is a novel imaging modality, first described by Muldoon et al. to present the system's construction and demonstrate its sub-cellular resolution imaging capabilities [43]. The HRME consists of three components: a thin-flexible fiber-optic probe, a combined light source and camera, and a laptop or tablet based processor [44]. It requires topical application of fluorescent contrast agents, such as proflavine, typically used at 0.01% concentration. The 3-m long probe has 30,000 individual optical fibers that total 1 mm in diameter; this probe is inserted through the accessory channel of a standard endoscope (similar to an endocytoscope or probe-based confocal microendoscope). Images are recorded by placing the distal tip of the fiber bundle into direct contact with the mucosa after application of the contrast agent, with each optical fiber acting as an individual pixel of the image. Illumination is provided by a battery powered 455 nm blue light-emitting diode (LED) transmitted through the imaging probe to the mucosal surface. The LED illumination excites the fluorophore, with the emitted light collected by the bundle and directed into a digital camera connected to the computer. This allows real-time mucosal imaging at subcellular resolution (4.4 μm), 1000× magnification and a frame rate of 12 fps. The field of view of the HRME depends on the diameter of the active area of the fiber bundle, usually 720 μm. The probe can be disinfected and reused approximately 60−75 times before the probe tip requires polishing. The advantages of this imaging technology include its portability, ease of use, and low cost, with current prototypes costing <$3500 in components.

This technology has been the subject of a number of studies investigating its use in screening and surveillance of a range of gastrointestinal neoplasia, including esophageal adenocarcinoma (EAC), esophageal squamous cell cancer (ESCC), colorectal neoplasia (CRC) and anal neoplasia. These studies have shown that HRME is a modality that consistently provides high sensitivity and specificity, negative predictive value, and accuracy across different diseases with rates comparable to those achieved with CLE. Table 1 highlights these results specifically for colorectal neoplasia. In addition, studies have illustrated that HRME users can be relatively easily trained in a short period of time and consistency across users via a solid inter-rater reliability [45].
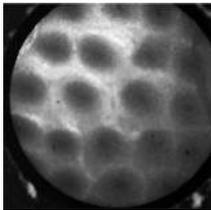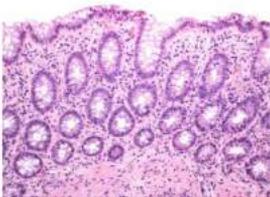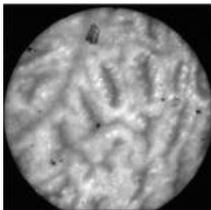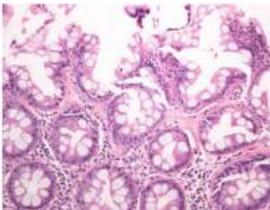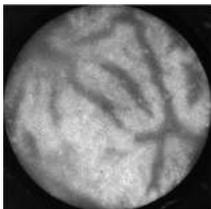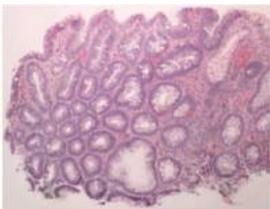
## HRME in colorectal neoplasia

Chang et al. developed a classification system for HRME to differentiate neoplastic from non-neoplastic colorectal polyps [46]. This criterion (Table 2) was established by two expert gastrointestinal pathologists who reviewed representative images from 68 patients with polyps who had undergone colonoscopy plus HRME. These images were correlated to their respective histopathologic diagnostic category of normal, hyperplastic, tubular adenoma, tubulovillous adenoma, or adenocarcinoma. In reviewing the HRME images, each pathologist noted the distinctive characteristics that corresponded to the histological features for each pathologic category, criteria that were glandular (size, shape, density), epithelial (thickness), and nuclear (size, arrangement). The pathologists then

**Table 1**
Accuracy of differentiation between neoplastic and non-neoplastic polyps, CLE versus HRME.

| Technology | Contrast | Field of view | Lateral resolution | Clinical results | | | |
|---|---|---|---|---|---|---|---|
| | | | | Study | Accuracy (%) | Sensitivity (%) | Specificity (%) |
| Confocal laser endoscopy (Pentax- eCLE) | - IV fluorescein<br>- Topical acriflavine 0.05% | 475 μm | 0.7 μm | Kiesslich et al. [35]<br>Hurlstone et al. [36] | 86−99 | 77−97 | 89−99 |
| Confocal laser endoscopy (Mauna Kea- pCLE) | - IV fluorescein<br>- Topical acriflavine 0.05% | 240−600 μm | 1 μm | Buchner et al. [37]<br>Kuiper et al. [38]<br>Shahid et al. [40] | 66−82 | 57−91 | 71−78 |
| HRME | Topical proflavine 0.01% | 750 μm | <4 μm | Parikh et al. [47] | 94 | 94 | 95 |

**Table 2**
HRME characteristics of colon polyps.

| Tissue diagnosis | Description | Example images (HRME [left] and histopathology [right]) |
|---|---|---|
| Normal Colonic Mucosa | - Regular appearance<br>- Symmetric glands of same size and shape throughout image<br>- No thickening of epithelium or lamina propria |  |
| Hyperplastic Polyp | - Serrated architecture<br>- Sawtooth glandular pattern |  |
| Tubular Adenoma | - Increased width of epithelium due to nuclear disordering and enlargement<br>- Narrowing of crypt lumen<br>- Wider and brighter epithelium<br>- "Picket fence" nuclei lining up perpendicular to crypt (larger nuclei with crowding)<br>- Increased epithelium to crypt ratio leading to crypt lumen narrowing |  |
| Colon Cancer | - Loss of normal crypt architecture<br>- Large, dense, overlapping, and pleomorphic nuclei |  |
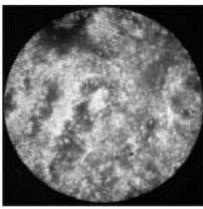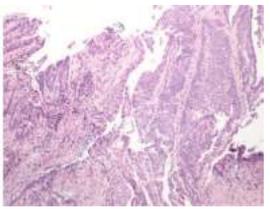
created consensus HRME imaging criteria descriptions based on the established World Health Organization histopathologic criteria applicable for each category. An HRME read of "non-neoplastic" was assigned to classification patterns for normal colonic mucosa, inflammatory or hyperplastic polyps. An HRME read of "neoplastic" included tubular adenoma, tubulovillous adenoma and adenocarcinoma.

They then validated this classification system by having seven endoscopists, four novice microendoscopists with no former HRME experience and three HRME experts (>50 cases) complete training and test sets of images to determine accuracy and interobserver variability. Expert microendoscopists identified neoplasia with sensitivity, specificity, and accuracy of 67%, 97%, and 87%. Non-experts achieved sensitivity, specificity, and accuracy of 73%, 91%, and 85%, respectively. Overall, neoplasia was identified with sensitivity 70%, specificity 94%, and accuracy 85%. Inter-observer agreement was high with Kappa values of 0.86 in experts; non-experts 0.72; and overall 0.78.

In-vivo studies built upon this body of data and further explored the utility of HRME in differentiating colonic neoplasia [47]. In a study by Parikh et al., 171 polyps from 94 patients, prospectively identified on routine colonoscopy were then imaged by HRME and classified in real-time as neoplastic (adenomatous, cancer) or non-neoplastic (normal, hyperplastic, inflammatory). HRME had a significantly higher accuracy (94%), specificity (95%), and positive predictive value (87%) for the determination of neoplastic colorectal polyps compared with WLE (65%, 39%, 55%). Additionally, the negative predictive value was high at 91.3%. Furthermore, this trend persisted in sub-analysis for both small (<10 mm) and diminutive polyps (<5 mm), with significantly better accuracy and specificity without a loss of sensitivity or negative predictive value. In particular, for diminutive polyps, HRME's accuracy (95%), specificity (98%), positive predictive value (93%), and negative predictive value (92.4%) were impressive.

Additionally, further studies demonstrated that endoscopists can be rapidly trained to interpret HRME images while maintaining high accuracy. In general, studies exploring the use of HRME noted that novice microendoscopists performed only slightly worse than experts in specificity and accuracy, with comparable sensitivity. This suggests that gastroenterologists who are new to HRME can be successfully and rapidly trained, in short periods of time, to use this technology with results similar to experts. A study done by Parikh et al. specifically investigated the learning curve associated with HRME device usage and image interpretation [48]. A total of 162 polyps from 97 patients were detected by WLE, imaged and evaluated by HRME and subsequently evaluated histologically. Forty-one percent (n = 67) of the polyps were neoplastic and fifty-three percent (n = 86) were smaller than 10 mm. Performance characteristics of HRME in differentiating neoplastic and non-neoplastic polyps were taken for the first 40 biopsies, the middle 40 biopsies, and then the last 82 biopsies. Sensitivity and specificity were 49.3% and 68.7%, respectively in the first 40 biopsies. Both measures improved to 93.6% and 91.5%, respectively, in biopsies 41 through 80. In the last 82 biopsies, HRME became even more sensitive (97.3%) and specific (95.5%). HRME's sensitivity and specificity significantly improved from the first interval of biopsies to the middle interval and from the first interval to the final interval. The improvement was maintained between the middle and final intervals. The PPV (positive predictive value) of the HRME was 88.2% in the middle set and 94.7% in the last set, both values being significantly greater than the PPV calculated for the first 40 biopsies (46.6%, p<0.04). Likewise, the NPV (negative predictive value) was only 71.9% for the first 40 biopsies but increased to 95.6% in the middle interval (p = 0.0278) and 97.7% in the last 82 biopsies (p = 0.0131). Additionally, HRME accuracy increased with each subsequent "optical" HRME biopsy taken. Accuracy was 62.5% in the first 40 biopsies and significantly increased to 92.5% in the middle set (p = 0.0032). The endoscopist remained highly accurate in HRME at 96.3% in the last 82 biopsies.

## Benefits of HRME

These studies have shown that the high levels of accuracy and specificity that HRME previously demonstrated in other forms of gastrointestinal neoplasia are maintained in evaluation of colonic neoplasia. In particular, the high accuracy of HRME, along with its high specificity and high negative predictive value for neoplasia in small and diminutive polyps, may allow the endoscopist to make enhanced, confident decisions regarding leaving small, non-neoplastic polyps in situ and discarding small polyps with low neoplastic potential. As noted before, this could potentially improve overall cost effectiveness of endoscopic surveillance in conditions such as Barrett's or ulcerative colitis, as surveillance biopsies account for significant cost per procedure.

Furthermore, HRME offers clinicians the ability to interrogate histologic features of suspicious lesions and evaluate post-resection margins in real-time during procedures. Such information can be used to make immediate clinical decisions at the point of care, potentially facilitating immediate minimally invasive therapies such as EMR, expediting margin determination during procedures, and reducing repeat procedures.

Though not yet investigated in any specific studies, the established grading criterion does differentiate between non-advanced adenomas and advanced adenomas with a villous component. This could be extremely valuable in the evaluation of diminutive polyps, as it can help identify those polyps

which are small but nevertheless advanced adenomas, and thus avoid mistakenly not being offered appropriate surveillance. Fig. 1 highlights the appearance of colon polyps on HRME as compared with the gold standard of histology.

Another strength of the HRME device lies in the high degree of inter-rater reliability among endoscopists of different experience for interpreting HRME images. This indicates an impressive and necessary consistency in HRME usage, and suggests that results may be reproducible in clinical practice.

Similarly, it has been specifically shown that a short training period is sufficient to achieve adequate competence in polyp discrimination using HRME. In fact, time to expertise, with >90% accuracy, as well as final sustained sensitivity, specificity and accuracy favored HRME compared to studies done in either probe-based and endoscope-based CLE systems [49,50]. Relatedly, the post-training accuracy values reached by the endoscopists who were not experts in HRME were not inferior to those shown by the HRME experts. This would in turn support the generalizability of HRME within the endoscopist community.

Finally, the straightforward optical design of the device requires no scanning mirrors, complex light sources, or other moving parts, and the device as a whole is small and portable. This translates into a significantly decreased cost for production and maintenance of the device. This also decreases the need for specialized maintenance and may enable its use in both areas with high levels of support and those with less infrastructure or resources, such as in third world countries, where other optical imaging technologies would not be available and cost-saving is even more important.

## Roadblocks and/or limitations

There are several current limitations to the HRME device. Firstly, proflavine, the most frequently utilized contrast agent, is currently an investigational drug. While no comprehensive long-term studies of proflavine have been published, proflavine-containing compounds, such as topical antiseptics, have been used extensively without reported mutagenic effects in humans. However, concerns regarding its use must be resolved prior to widespread use in practice, else a different contrast agent will need to be investigated and verified.

An additional limitation is the probe's inability to image subsurface regions. The current HRME device yields images by placing the device tip into direct contact with tissue, limiting image acquisition to the superficial epithelium. However, the fiber-optic probe is small enough to pass through the lumen of a 16-gauge needle which could be used to penetrate into deeper layers of the epithelium, allowing imaging of these areas, though this has yet to be explored in clinical trials.
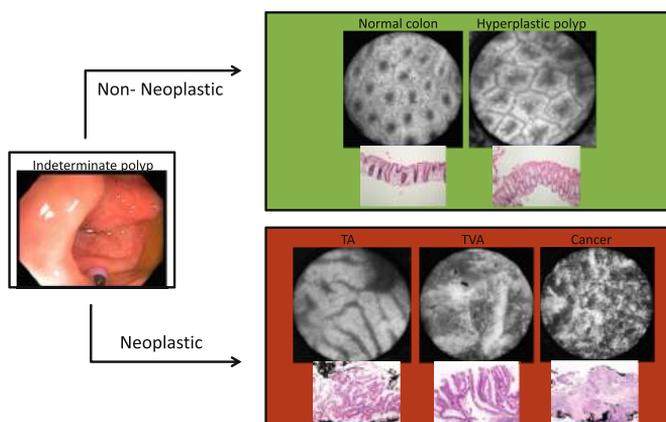


**Fig. 1.** Reproduced from Parikh ND et al. In vivo diagnostic accuracy of high-resolution microendoscopy in differentiating neoplastic from non-neoplastic colorectal polyps: a prospective study. Am J Gastroenterol.2014; 109(1):68–75.

Another drawback is its limited field of view. Consequently, alone, HRME can only sample a small fraction of the mucosa at a time, presenting challenges, especially in heterogeneous regions of tissue. One solution lies in coupling the HRME with a widefield imaging system. If paired with a suitably sensitive widefield platform, such a combination would be able to rapidly survey large mucosal surfaces, identify suspicious areas, and subsequently interrogate those regions with high resolution. Another recently developed technique is video mosaicing, where consecutive video frames are stitched together as the probe advances along tissue [51]. This creates compiled images from areas much larger than a single field of view.

Relatedly, the use of the HRME device does add time to the length of procedures. Preliminary results in esophageal surveillance show that additional procedure length can range from 2 to 25 minutes depending on the size of the area of interest and the experience of the operator. Though this may limit its use in conditions with large areas to survey, this additional time may also be mitigated by coupling the HRME with a widefield system.

Though the HRME device has demonstrated high accuracy and specificity, there have not been trials directly comparing it against other high-sensitivity imaging technologies such as confocal and narrow band imaging in the colon. Additional comparative studies will need to be done to accurately compare the performance and diagnostic yield of HRME to other optical imaging modalities. Similarly, there have been no studies specifically investigating the use of this device in specific high risk populations such as with inflammatory bowel disease (IBD).

Finally, there has not been any specific diagnostic criterion established for alternative polyp types, in particular sessile serrated adenomas (SSA's). There was a brief mention of SSA's in the Parikh et al. study, which happened to include seven of these polyps. In that study the HRME had a sensitivity of 85.7% and a specificity of 100% for classifying SSAs as neoplastic polyps. However, given the limited sample size, it is difficult to confidently derive the specific HRME characteristics for SSAs, though they tended to have more distorted glands and a greater epithelial to crypt space ratio compared to hyperplastic polyps while not having the linear crypts or elongated nuclei seen typically in tubular adenomas. Further investigation into the HRME characteristics of SSAs is warranted.

## HRME future directions

Though the benefits of the HRME device are numerous, future studies are still needed in order to validate the clinical applicability of the technology, as well as to more fully explore its use with different colonic lesions and disease states. In particular, the development of diagnostic criterion for colonic lesions not yet well-described, such as SSAs, is important before its use can be fully advocated. In addition, the future exploration of other alternative fluorescent contrast agents will further assist in answering some of the current limitations of the technology.

Additionally, studies investigating the use of HRME in surveillance of other premalignant conditions, specifically inflammatory bowel disease, may also validate its viability in such situations. Because of the large number of biopsy specimens, surveillance colonoscopy in inflammatory bowel disease, especially ulcerative colitis (UC), is currently time consuming and significant flat lesions still may be missed. Novel endoscopic techniques, like confocal laser endomicroscopy, have been shown to increase neoplasia detection rates with fewer biopsies required; Kiesslich et al. [35] demonstrated a 4.75 fold increase in neoplasia detection (with 50% fewer biopsies) in UC patients undergoing surveillance colonoscopy with CLE (with chromoscopy) as compared with conventional colonoscopy. As discussed previously, HRME can offer similar sensitivity and specificity to CLE in differentiating between neoplastic and non-neoplastic lesions at a fraction of the cost. Furthermore, HRME is highly applicable to gastroenterologists across a variety of clinical settings. Studies validating HRME use for surveillance in IBD may prove extremely beneficial in this population. Randomized trials directly comparing HRME to other high resolution modalities, like CLE, will be vital to further validate HRME's efficacy as a classification modality for colorectal neoplasia. Finally, further applications for exploration may include use of HRME for the assessment of margins for lesion resection, as well as other diagnostic procedures.

With regards to the "resect and discard" strategy, the strong diagnostic capabilities of the HRME device make it ideal for the application of this strategy [52]. Current studies have validated that the HRME device satisfies the officially recommended minimum criteria for incorporation of advanced endoscopic imaging into clinical practice, defined by the PIVI ("Preservation and Incorporation of Valuable endoscopic Innovations") statement of the American Society for Gastrointestinal Endoscopy (ASGE) as a 90 % agreement with post-histological surveillance recommendations and a >90 % negative predictive value for diminutive adenomatous histology. HRME takes advantage of distinct morphologic characteristics of the lesions themselves, namely the subcellular epithelial pattern. This provides a complementary data set, rather than duplicate, as at the current literature focuses primarily on ECE, which mainly looks at vascular patterns. Thus, HRME could be paired with ECE, functioning as a widefield imaging platform, thereby making optimal use of the high specificity of the technique and supplementing the relatively low specify which was demonstrated when an ECE-based resect and discard strategy was implemented by community-based endoscopists [33]. This high specificity of HRME could prevent substantial overuse of endoscopic surveillance by correctly reclassifying some true negatives. HRME relatively cheap design also supports a technical and economical feasibility. Finally, a main limitation of ECE evaluation is an inability to discriminate between advanced and nonadvanced adenomas; this means that a few patients with diminutive but nevertheless advanced adenomas would mistakenly not be offered appropriate surveillance. If the validity of Chang et al.'s classification were to be confirmed in future studies, HRME could help to avoid an overlong surveillance interval in those with tubulovillous diminutive lesions, simply characterized as "adenomatous" at ECE, by correctly reclassifying such lesions as "advanced".

## Conclusion

The high resolution microendoscopy is a novel technology that, while still in the early stages of investigation of its use in gastrointestinal neoplasia, has already demonstrated significant diagnostic accuracy and potential efficacy in the differentiation of neoplastic from non-neoplastic colorectal polyps. HRME's high accuracy, specificity, and negative predictive value for neoplastic polyps are comparable not only to high-definition WLE but also to other advanced imaging modalities, making it a very attractive complementary tool. This new modality has the potential to reduce procedure-related costs, not only by virtue of its low cost components, but also by decreasing procedure time, biopsy number, return visits, and its possibly application into the resect-and discard strategy. Furthermore, such cost-effective, portable devices can potentially help fill gaps in settings where the infrastructure to support traditional endoscopy and pathology services are either not available or affordable. Further investigations are warranted to determine the ideal widefield technology to complement HRME, directly compare it to other optical biopsy technologies, as well as further expand its diagnostic capabilities in high risk populations.

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**Practice points**

- Colon cancer remains one of the leading causes of death in the United States
- Early detection of adenomas and premalignant lesions prevents progression to advanced stage colorectal cancer
- Novel endoscopic technologies are enhancing the power of colonoscopy to achieve "optical biopsy" of colon polyps
- High-resolution microendoscopy is a low-cost, widely applicable technology allowing real-time histologic evaluation of polyps
- HRME can increase the ability to pursue a "resect and discard" polyp resection strategy or reduce unnecessary polypectomies all together

**Research agenda**

- Future studies can evaluate the role of HRME for surveillance of premalignant conditions such as inflammatory bowel disease
- Further development of criteria for identification of uncommon polyps like sessile serrated adenomas will expand the ability of HRME to differentiate neoplastic from non-neoplastic polyps
- Alternative fluorescent contrast agents can be develop to continue to improve the ability of HRME to detect mucosal abnormalities
- The next step will be to assess the use of HRME in community-based gastroenterology practices

## Conflict of interest statement

There is no conflict of interest for any of the authors of this publication.

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