Advanced endoscopic imaging: European Society of Gastrointestinal Endoscopy (ESGE) Technology Review

Background and aim: This technical review is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE). It addresses the utilization of advanced endoscopic imaging in gastrointestinal (GI) endoscopy.

Methods: This technical review is based on a systematic literature search to evaluate the evidence supporting the use of advanced endoscopic imaging throughout the GI tract. Technologies considered include narrowed-spectrum endoscopy (narrow band imaging [NBI]; flexible spectral imaging color enhancement [FICE]; i-Scan digital contrast [I-SCAN]), autofluorescence imaging (AFI), and confocal laser endomicroscopy (CLE). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was adopted to define the strength of recommendation and the quality of evidence.

Main recommendations:

1. We suggest advanced endoscopic imaging technologies improve mucosal visualization and enhance fine structural and microvascular detail. Expert endoscopic diagnosis may be improved by advanced imaging, but as yet in community-based practice no technology has been shown consistently to be diagnostically superior to current practice with high definition white light. (Low quality evidence.)

2. We recommend the use of validated classification systems to support the use of optical diagnosis with advanced endoscopic imaging in the upper and lower GI tracts (strong recommendation, moderate quality evidence).

3. We suggest that training improves performance in the use of advanced endoscopic imaging techniques and that it is a prerequisite for use in clinical practice. A learning curve exists and training alone does not guarantee sustained high performances in clinical practice. (Weak recommendation, low quality evidence.)

Conclusion: Advanced endoscopic imaging can improve mucosal visualization and endoscopic diagnosis; however it requires training and the use of validated classification systems.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFI</td>
<td>autofluorescence imaging</td>
</tr>
<tr>
<td>BING</td>
<td>Barrett’s International NBI Group</td>
</tr>
<tr>
<td>CAD</td>
<td>computer-aided diagnosis</td>
</tr>
<tr>
<td>CCD</td>
<td>charge-coupled device</td>
</tr>
<tr>
<td>CE</td>
<td>contrast enhancement</td>
</tr>
<tr>
<td>CLE</td>
<td>confocal laser endomicroscopy</td>
</tr>
<tr>
<td>ESGE</td>
<td>European Society of Gastrointestinal Endoscopy</td>
</tr>
<tr>
<td>FICE</td>
<td>flexible spectral imaging color enhancement (also termed Fujinon Intelligent Chromo Endoscopy)</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>I-SCAN</td>
<td>i-Scan digital contrast</td>
</tr>
<tr>
<td>I-SCAN</td>
<td>integrated confocal laser endomicroscopy</td>
</tr>
<tr>
<td>IPCL</td>
<td>intrapapillary capillary loop</td>
</tr>
<tr>
<td>JNET</td>
<td>Japanese NBI Expert Team</td>
</tr>
<tr>
<td>NADPH</td>
<td>nicotinamide adenine dinucleotide phosphate</td>
</tr>
<tr>
<td>NBI</td>
<td>narrow band imaging</td>
</tr>
<tr>
<td>NICE</td>
<td>NBI International Colorectal Endoscopic</td>
</tr>
<tr>
<td>pCLE</td>
<td>probe-based confocal laser endomicroscopy</td>
</tr>
<tr>
<td>SE</td>
<td>surface enhancement</td>
</tr>
<tr>
<td>SIM</td>
<td>specialized intestinal metaplasia</td>
</tr>
<tr>
<td>TE</td>
<td>tone enhancement</td>
</tr>
<tr>
<td>WASP</td>
<td>Workgroup serrAted polypS and Polyposis</td>
</tr>
<tr>
<td>WLE</td>
<td>white-light endoscopy</td>
</tr>
</tbody>
</table>

IBD | inflammatory bowel disease |

Authors

James E. East1, Jasper L. Vleugels2, Philip Roelandt3, Pradeep Bhandari1, Raf Bisschops1, Evelien Dekker2, Cesare Hassan5, Gareth Horgan6, Ralf Kiesslich7, Gaius Longcroft-Wheaton4, Ana Wilson8, Jean-Marc Dumonceau9

Institutions

Institutions are listed at end of article.

Bibliography

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Corresponding author
James E. East, MD (Res) FRCP
Translational Gastroenterology Unit, Experimental Medicine Division
Nuffield Department of Clinical Medicine, University of Oxford
John Radcliffe Hospital
Headley Way, Headington
Oxford, OX3 9DJ
United Kingdom
Fax: +44-1865-228763
james.east@ndm.ox.ac.uk

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1. Introduction

Since the introduction of flexible gastrointestinal (GI) endoscopy in the 1960s there has been a relentless advance in endoscopic imaging technology to assist clinicians to make better decisions. Initially this focused on the replacement of fiberoptics by a charge-coupled device (CCD) to acquire images and then on images of higher resolution. In the 1970s, the use of dye-spray to stain the mucosa was introduced in Japan to aid diagnosis and was called “chromoendoscopy” [1]; however this has not been widely accepted by Western endoscopists, despite diagnostic advantages, as it is time-consuming and has a significant learning curve [2]. In the last 10 years a series of “push-button” technologies (e.g. narrowed-spectrum endoscopy and autofluorescence imaging [AFI]) have allowed advanced endoscopic imaging to be available more simply; concurrently confocal laser endomicroscopy (CLE) has allowed endoscopists to obtain “in vivo histology” [3]. Nevertheless, to be effective all the available imaging technologies require basic endoscopic elements such as high quality bowel preparation and dexterous operators, with appropriate training.

A previous ESGE Guideline has recently focused on the diagnostic performance of these technologies in the colon [4]. The current complementary technological review working group systematically reviewed the literature on these technologies throughout the GI tract and used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to define the strength of any recommendation and the quality of evidence [5], with multiple review rounds. This review aims to set out how the technologies work, how to implement them, and where they are best used in the GI tract; if they offer no or limited benefit this is also stated. Because of the scope of the review only key references on clinical utility are presented.

1.1 Narrowed-spectrum technologies

Narrowed-spectrum endoscopy is so called because this group of image enhancement techniques relies on using only a narrowed part of the available spectral bandwidth, mainly corresponding to “blue light.” This is accomplished through optical or digital filtering and has also been termed “virtual chromoendoscopy.” All major manufacturers now offer this functionality built into endoscopic systems as standard. High definition is a prerequisite to optimal usage of these technologies.

1.1.1 Narrow band imaging

Narrow band imaging (NBI) (Olympus Medical Systems, Tokyo, Japan) was the first of the commercially available narrowed-spectrum technologies. NBI functions by filtering the illumination light. The red component of the standard red, green, and blue (RGB) filters is discarded and the spectral bandwidth of the blue and green light filters, centered on 415 and 540 nm, respectively, is reduced from 50–70 nm to 20–30 nm. The incoming signals from the charge-coupled device (CCD) are combined by the video processor to produce a false-color image. Hemoglobin absorbs the blue light; furthermore these shorter wavelengths penetrate the mucosa less deeply than red light which presents a wavelength of 650 nm [6]. This results in an increased contrast

<table>
<thead>
<tr>
<th>Technique</th>
<th>Company</th>
<th>Name</th>
<th>Geographic distribution</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrow band imaging (NBI)</td>
<td>Olympus</td>
<td>Lucera Spectrum/Exera Elite</td>
<td>Japan, UK</td>
<td>Video System Center (CV-260SL; Spectrum) (CV-290; Elite)</td>
</tr>
<tr>
<td>Flexible spectral imaging color enhancement (FICE)</td>
<td>Fujifilm</td>
<td>EPX-4400 system</td>
<td>Worldwide</td>
<td>XL-4400 light source; VP-4400 HD processor</td>
</tr>
<tr>
<td>i-Scan digital contrast (i-SCAN)</td>
<td>Pentax</td>
<td>EPK-i</td>
<td>Worldwide</td>
<td>Combined processor and light source in: EPK-i7000 HD processor (high end, fully adjustable interface) EPK-i5000 HD processor (i-SCAN presets, not custom-adjustable)</td>
</tr>
<tr>
<td>Blue laser imaging (BLI)</td>
<td>Fujifilm</td>
<td>Lasereo</td>
<td>Japan, China, South America, Asia-Pacifc</td>
<td>Processor VP-4450HD, Laser Light Source LL-4450 and LS90 series endoscopes</td>
</tr>
<tr>
<td>Autofluorescence imaging (AFI)</td>
<td>Olympus</td>
<td>Lucera Spectrum</td>
<td>Japan, UK</td>
<td>Video System Center (CV-260SL), CFH260 colonoscope A2ZL</td>
</tr>
<tr>
<td>Confocal laser endoscopy (CLE)</td>
<td>Pentax</td>
<td>Worldwide</td>
<td>Pentax ISC-1000 endomicroscopy system; EC3870K endoscope</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mauna Kea</td>
<td>Cellvizio</td>
<td>Worldwide</td>
<td>Cellvizio 100 series system; GastroFlex and ColoFlex UHD probes</td>
</tr>
</tbody>
</table>
for superficial microvessels which appear brown/black and in
greater clarity of mucosal surface structures [7].
In Japan and in the United Kingdom, NBI systems with a mono-
chrome CCD (Lucera, "200" series) are predominantly used; in
the rest of the world NBI systems with a color CCD (Exera, "100"
series) are used (Table 1).

### 2.1.2 Flexible spectral imaging color enhancement

Flexible spectral imaging color enhancement (FICE) (Fujinon In-
elligent Chromo Endoscopy; Fujifilm, Tokyo, Japan) is a post-
processor technology for vascular and surface tissue image en-
hancement [8]. Unlike NBI, which utilizes physical optical light
filters, FICE selects particular wavelengths from digitized data.
The color intensity spectrum for each pixel of the white-light im-
age is analyzed in a "spectral estimation" circuit in the video pro-
cessor. Images can then be reconstructed, pixel by pixel, using
only a single selected wavelength. Three such single-wavelength
images are selected and assigned to the red, green, and blue
monitor inputs to display a composite color-enhanced image in
real time. This can be used like NBI to remove data from the red
part of the waveband and to narrow the green and blue spectra.
However, the system is flexible. It has 10 preset digital filter set-
tings with the ability to program more (Table 2) [9].

### 2.1.3 i-Scan digital contrast (I-SCAN)

I-SCAN (Pentax, Tokyo, Japan) is another post-processing digital
contrast technology that consists of three enhancement features:
surface enhancement (SE), which sharpens the image; contrast
enhancement (CE) where darker (depressed) areas look more
blue; and tone enhancement (TE), a form of digital narrowed-
spectrum imaging. TE has some similarities to FICE, in that the
white-light image is split into its red, green, and blue compo-
ents. Each component can then be independently modified,
this being followed by recombination of the three components
to construct a new digital image. Originally, four different types
of TE modification, to enhance different mucosal structures,
were available: TE-v for vascular pattern assessment, which is
no longer used; TE-c for the intestine; TE-e for the esophagus;
and TE-g for the stomach [10].

Three standardized I-SCAN settings are now readily available in
the factory settings of the processor, including I-SCAN 1 (SE) re-
commended for detection, I-SCAN 2 (combination of SE and TE-c)
recommended for lesion characterization, and I-SCAN 3 (combi-
nation of SE, TE-c, and CE) recommended for lesion demarcation,
with I-SCAN 2 being probably the most widely used.

### 2.2 Autofluorescence imaging

Some natural tissue molecules, such as collagen, flavins, and ni-
cotinamide adenine dinucleotide phosphate (NADPH), are fluor-
ophores, that is, they emit fluorescence after excitation with
short-wavelength light. Autofluorescence imaging (AFI; Olympus)
is based on real-time detection of such fluorescence. The
AFI signal is altered by changes in mucosal thickness, in mucosal
blood flow, and in the endogenous tissue fluorophores. Thick tis-

**Table 2** Preset wavelengths and gain for flexible spectral imaging color enhancement (FICE; also Fujinon Intelligent Chromo Endoscopy). By kind permission of Fujifilm Europe GmbH.

<table>
<thead>
<tr>
<th>Preset</th>
<th>Wavelength in nm (Gain)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Red</td>
<td>525 (3)</td>
</tr>
<tr>
<td>Green</td>
<td>495 (4)</td>
</tr>
<tr>
<td>Blue</td>
<td>495 (3)</td>
</tr>
</tbody>
</table>
Unlike narrowed-spectrum technologies or AFI, CLE requires contrast agents. The most commonly used dyes are fluorescein administered intravenously and acriflavine and cresyl violet which are applied topically [17, 19, 20].

2.4 Other technologies
The usefulness of most narrowed-spectrum technologies can be limited by a dark field of view. Blue laser imaging (BLI) (Lasereo; Fujifilm, Kanagwa, Japan), may overcome this limitation by combining two laser light sources of wavelengths 410nm and 450nm. The 450-nm laser strikes a phosphor, inducing fluorescent light that is equivalent to a xenon light source. The other laser provides enhanced mucosal surface information by applying a limited wavelength spectrum of 410-nm blue light, similarly to other narrowed-spectrum technologies. In a tandem endoscopy study in 39 patients in which the visibility provided by BLI and NBI was compared, the mean observable distance was significantly higher for BLI compared with NBI [21]. Promising early data are also available for characterization of small (<10mm) colonic polyps and for assessing invasiveness of colonic lesions, but large multicenter experience and validation is awaited [22, 23]. This technology is not available in Europe, but a similar technology using light-emitting diodes instead of lasers may soon become commercially available.

The Storz professional image enhancement system (SPIES; Karl Storz, Tuttingen, Germany) is another post-processing digital contrast technology that has some similarities to I-SCAN and FICE. No published data are available for the GI tract. Given the lack of available clinical data, BLI and SPIES will not be considered further in this review.

3 Optical diagnosis classification systems

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**Table 3** Technical aspects of confocal laser endomicroscopy (CLE) systems [18].

<table>
<thead>
<tr>
<th>Endoscope-based</th>
<th>Probe-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outer diameter, mm</td>
<td>12.8 (scope)</td>
</tr>
<tr>
<td>Length, cm</td>
<td>120; 180</td>
</tr>
<tr>
<td>Field of view, μm²</td>
<td>475 × 475</td>
</tr>
<tr>
<td>Resolution, μm</td>
<td>0.7</td>
</tr>
<tr>
<td>Magnification</td>
<td>×1000</td>
</tr>
<tr>
<td>Imaging plane depth, μm</td>
<td>0 – 250 (dynamic)</td>
</tr>
</tbody>
</table>

* Reprinted from [18], Copyright 2013, with permission from Elsevier.
† Dependent on various probes.

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2. We recommend the use of validated classification systems to support the use of optical diagnosis with advanced endoscopic imaging in the upper and lower GI tracts (strong recommendation, moderate quality evidence).
3.1 Narrowed-spectrum endoscopy and optical diagnosis

3.1.1 Upper GI tract

**Squamous cell carcinoma.** Squamous cell dysplasia or carcinoma appears as dark brown patches on the esophageal mucosa. The intrapapillary capillary loop (IPCL) classification, also called the Inoue classification has been developed to enable endoscopic assessment of the likely depth of invasion using NBI and magnification [24–26]. Increasing dilatation and tortuosity of the IPCLs is associated with higher grade of dysplasia (Fig. 1).

**Barrett’s esophagus.** NBI has been applied in Barrett’s esophagus to enhance the targeting of both intestinal metaplasia and dysplasia. For NBI in conjunction with magnification, three main classification systems have been proposed, from Kansas, Amsterdam, and Nottingham (Table 4) [27–29]. These suggest that irregular mucosal pattern and vessels are predictive of dysplasia, and the “ridged/villous” pattern is predictive of specialized intestinal metaplasia (SIM). In one study that compared all three systems, accuracy for nondysplastic SIM ranged between 57% and 63% and for dysplasia the accuracy was 75% [30]. Interobserver agreement was fair (Nottingham classification) to moderate (Kansas and Amsterdam classifications).

More recently a simpler classification system to discriminate neoplastic from non-neoplastic Barrett’s esophagus using NBI has been developed and validated. The Barrett’s International NBI Group (BING) used near-focus technology, but not formal magnification endoscopy, with encouraging results (Table 4, Fig. 2) [31].

**Gastric intestinal metaplasia and dysplasia.** For gastric lesions examined with NBI some features are similar to those seen in Barrett’s esophagus, with regular mucosal and vascular patterns favoring the absence of dysplasia, and ridged or villous patterns being found in areas that are suggestive of intestinal metaplasia. The “light blue crest” sign, not seen in Barrett’s esophagus, is relatively specific for gastric intestinal metaplasia but its absence does not exclude intestinal metaplasia (Fig. 3, Video 1) [32]. Variable vascular density may indicate the presence of Helicobacter pylori infection. A proposed combined classification system is shown in Table 5 [33].

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**Table 4** Classification systems for Barrett’s esophagus with magnification-narrow band imaging (NBI) [30].

<table>
<thead>
<tr>
<th></th>
<th>Kansas [27]</th>
<th>Amsterdam [28]</th>
<th>Nottingham [29]</th>
<th>Barrett’s International NBI Group (BING) [31]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>Mucosal pattern: circular</td>
<td>Mucosal pattern: regular</td>
<td>Type A: round/oval pits with regular microvasculature</td>
<td>Mucosal pattern: circular, ridged/villous, or tubular</td>
</tr>
<tr>
<td></td>
<td>Vascular pattern: normal</td>
<td>Vascular pattern: regular</td>
<td></td>
<td>Vascular pattern: blood vessels situated regularly along or between mucosal ridges and/or those showing normal, long, branching patterns</td>
</tr>
<tr>
<td><strong>Intestinal metaplasia</strong></td>
<td>Mucosal pattern: ridged/villous</td>
<td>Mucosal pattern: regular (villous/gyrus)</td>
<td>Type B: villous/ridge/linear pits with regular microvasculature</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vascular pattern: normal</td>
<td>Abnormal blood vessels: absent</td>
<td>Type C: absent pits with regular microvasculature</td>
<td></td>
</tr>
<tr>
<td><strong>Dysplasia</strong></td>
<td>Mucosal pattern: irregular</td>
<td>Mucosal pattern: irregular</td>
<td>Type D: distorted pits with irregular microvasculature</td>
<td>Mucosal pattern: absent or irregular patterns</td>
</tr>
<tr>
<td></td>
<td>distored</td>
<td>Vascular pattern: irregular</td>
<td></td>
<td>Vascular pattern: focally or diffusely distributed vessels not following normal architecture of the mucosa</td>
</tr>
<tr>
<td></td>
<td>Vascular pattern: abnormal</td>
<td>Abnormal blood vessels: present</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.1.2 Lower GI tract

Machida et al. [7] described NBI visualization of the microvessel network as a way of differentiating between neoplastic and non-neoplastic lesions; Hirata et al. [34] were the first to describe vessel thickness as seen with NBI as a way of assessing the histological grade and depth of invasion of colorectal tumors. NBI measurements of the microvascular density (meshed capillary vessels, vascular pattern intensity, or brown hue) present an accuracy for colonic polyp characterization similar to that of magnified chromendoscopic assessment based on Kudo’s pit pattern classification [35–37]. However, both the lesion color and vessel thickness are subjective estimates. This has led to the consensus-based development of the NBI International Colorectal Endoscopic (NICE) classification system, based on color, vessels, and surface pattern criteria, for the endoscopic diagnosis of small colonic polyps [38] (Table 5).

### Table 5

<table>
<thead>
<tr>
<th>Proposed classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
</tr>
<tr>
<td>Mucosal pattern</td>
</tr>
<tr>
<td>Vascular pattern</td>
</tr>
<tr>
<td>Expected outcome</td>
</tr>
</tbody>
</table>

A subsequent development of the NICE classification is the Japanese NBI Expert Team (JNET) classification [40]. This requires magnification and subdivides adenomatous lesions (NICE type 2) into type 2A, namely low grade adenomas, and type 2B, high grade adenomas including shallow submucosally invasive cancer. The World Endoscopy Organization has included the JNET classification in the next version of its “minimal standard terminology” (MST; version 4.0), used in endoscopic reporting systems; however the JNET classification has not had widespread international validation and the increased complexity and need for magnification may restrict adoption by community-based endoscopists.

Sessile serrated polyps, recently recognized as precursor lesions of colorectal cancer [41], are not incorporated in the NICE classification. The “Workgroup serrAted polyPSS and Polyposis” (WASP) classification combines the NICE classification and four sessile serrated lesion-like features, namely, cloud-like surface, indistinct...
border, irregular shape, and dark spots inside the crypts (Fig. 4 and Fig. 5). The presence of at least two features is considered sufficient to diagnose a sessile serrated lesion. During the validation phase, optical diagnosis made with high confidence showed a pooled accuracy of 84% and pooled negative predictive value of 91% for diminutive neoplastic lesions [42].

I-SCAN classification systems for polyps have also been developed using pit patterns and microvessel features (Fig. 6). Bouwens et al. [43] developed a simple system, termed the “i-scan classification for endoscopic diagnosis” (ICE), and based on the Kudo and NICE classifications, in which color, epithelial surface pattern, and vascular pattern were independently rated. A total of 11 nonexpert endoscopists were trained on I-SCAN optical diagnosis using a didactic training session and a training module. Afterwards they evaluated still images of 50 polyps, and the mean sensitivity, specificity, and accuracy for the diagnosis of adenomas were 79%, 86%, and 81%, respectively. Of the diagnoses, 81% were made with high confidence and these were associated with a significantly higher diagnostic accuracy compared with the remaining diagnoses.

For FICE (Fig. 7), the classification by Teixeira et al. was described in 2009 and was based on magnified microvessel patterns:

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Same or lighter than background</td>
<td>Brown relative to background (verify that color arises from vessels)</td>
</tr>
<tr>
<td>Vessels</td>
<td>None or isolated lacy vessels coursing across the lesion</td>
<td>Brown vessels surrounding white structures</td>
</tr>
<tr>
<td>Surface pattern</td>
<td>Dark or white spots of uniform size, or homogeneous absence of pattern</td>
<td>Oval, tubular, or branched white structures surrounded by brown vessels</td>
</tr>
<tr>
<td>Most likely pathology</td>
<td>Hyperplastic</td>
<td>Adenoma</td>
</tr>
</tbody>
</table>

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**Video 1**

Atrophic gastric body seen with white light with possible depressed, reddened area. Switch to narrow band imaging (NBI) reveals multiple pale areas suspicious for intestinal metaplasia. Subsequent magnification shows the “light blue crest” sign, confirming intestinal metaplasia. Nearby, the depressed area is shown to contain an area of irregular microvessels surrounded by a demarcation line, highly suspicious for early gastric cancer. (Video courtesy of Dr. Noriya Uedo, Osaka, Japan). Online content including video sequences viewable at: http://dx.doi.org/10.1055/s-0042-118087

**Video 2**

Narrow band imaging International Colorectal Endoscopic (NICE) classification for colorectal polyps [38]. Assessment of a small colonic polyp using narrow band imaging (NBI) and near focus. The polyp is seen to have a dark color compared to the background mucosa, and white tubular structures surrounded by brown vessels; therefore it is a type 2 polyp—adenoma. Note lack of Workgroup serrAted polypS and Polyposis (WASP) classification features (see Fig. 4). Online content including video sequences viewable at: http://dx.doi.org/10.1055/s-0042-118087
types I and II show few, short, straight, and sparsely distributed vessels; and types III to V have numerous, elongated, and tortuous capillaries that are irregularly distributed. This classification provides good diagnostic accuracy for colonic polyps [44]. The assessment of observations made by two endoscopists using this classification suggests that agreement is very good (interobserver agreement 0.80; intraobserver agreement 0.73 and 0.88) [45]. Notably, a study that applied the NICE classification (which was developed for NBI) to videos of polyps recorded using FICE in order to differentiate adenomas from hyperplastic polyps showed an accuracy of only 77%, with only modest interobserver and intraobserver agreement (0.51 and 0.40, respectively). This suggests that classification systems may not be interchangeable between advanced imaging modalities [46].

3.2 Autofluorescence imaging and optical diagnosis

For optical diagnosis in the colon, an algorithm has been developed [47]: if the lesion of interest is colored purple this would indicate neoplastic tissue (Fig. 8); if it is green, this indicates non-neoplastic tissue; and if it is violet (in-between), NBI should be used for further discrimination.

In Barrett's esophagus, accuracy for diagnosing dysplasia using AFI was 69%–76%, and this was further improved if high resolution white-light endoscopy (WLE) images were also available; interobserver agreement was fair to moderate [48].

3.3 Confocal laser endomicroscopy and optical diagnosis

The Mainz classification (Table 7, Fig. 9) was the first formal classification system for iCLE for colonic polyps that differentiated normal, regenerative, and dysplastic epithelium [12]. This has demonstrated high levels of accuracy, and interobserver as well as intraobserver agreements appeared to be substantial in one study that included three observers (0.68–0.84) [49]. The Miami classification was proposed in 2009 for pCLE covering both the upper and lower GI tracts, with dysplasia being associated with a dark, irregular, thickened epithelium [50]. In a pilot study in Barrett's esophagus, accuracy and interobserver agreement were high, and similar results were reported for in a pilot study for colonic polyps; however numbers of patients in both studies were very small [51, 52].
3. We suggest that training improves performance in the use of advanced endoscopic imaging techniques and that it is a prerequisite for use in clinical practice. A learning curve exists and training alone does not guarantee sustained high performances in clinical practice. (Weak recommendation, low quality evidence.)

4. Training to achieve competence

4.1 Upper GI tract: training

4.1.2 NBI

For NBI with magnification, a 2-hour training session in the IPCL (abnormal intrapapillary capillary loops) classification improved diagnostic accuracy for both beginners and less experienced endoscopists, with the latter reaching the performance of highly experienced endoscopists. Training also improved interobserver agreement [53]. Baldaque-Silva et al. [54] were the first authors to report on the use of a structured learning program, using videos with continuous histological feedback, for the endoscopic classification of Barrett’s esophagus using high magnification NBI and the Amsterdam criteria [28]; there was no improvement in diagnostic accuracy or interobserver agreement and these were suboptimal throughout the study.

In the stomach, Dias-Silva et al. [55] assessed the learning curve when using NBI without magnification to diagnose precancerous lesions. After an initial training module, feedback was given a week after answers were submitted, via a web-based learning system, for 20 tests each comprising 10 NBI videos. For all endoscopists global accuracy increased throughout the learning program, from 60% for the first quartile to 70% for the last one, as did specificity.

4.1.3 CLE

For CLE also, a learning curve was found for the diagnosis of esophageal squamous cell carcinoma [56], and for intestinal metaplasia in the stomach [57].

4.2 Lower GI tract: training

4.2.1 NBI

A number of training modules have been developed to improve accuracy of optical diagnosis using NBI. Initial training in NBI, using still images and either expert classroom training session or a validated PowerPoint presentation, was found to improve both the accuracy and interobserver agreement of optical diagnosis among endoscopists of various levels of experience [58, 59]. Studies using still images and NBI with magnification had similarly shown improvement in diagnostic accuracy following training [60, 61]. However still images are a poor representation of routine clinical practice, where multiple views of the polyp are obtained from...
4.2 Other advanced imaging modalities

4.2.2 Other advanced imaging modalities

Similar improvements in diagnostic performance have been reported with either classroom lecture or online training for I-SCAN [43]. Neumann et al. [64] showed in a study of the learning curve of I-SCAN that the overall diagnostic accuracy improved from 74% for the first quartile of polyp images to 94% for the last one.

For CLE also a learning curve was reported with accuracy improving after training, from 63% for the first quartile of polyp images to 86% for the last quartile [65].

5. Decision support tools and computer-aided diagnosis

Several groups of authors have developed computer-aided diagnosis (CAD) systems to help with colorectal polyp characterization. Tischendorf et al. [66] reported a first prospective clinical study where a computer-based system used vascular features as observed with NBI and involved image preprocessing, vessel segmentation, feature extraction, and classification. The diagnostic performance of such algorithms has been improved so that they now match human performance (Table 8; [66–71]). Similar software has been developed for CLE with performance equivalent to that of human experts [67].

Table 7 Mainz classification for the assessment of colonic lesions using confocal laser endoscopy (CLE) [12].†

<table>
<thead>
<tr>
<th>Grade</th>
<th>Vessel architecture</th>
<th>Crypt architecture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Hexagonal, honeycomb appearance</td>
<td>Regular luminal openings, homogeneous layer of epithelial cells</td>
</tr>
<tr>
<td>Regeneration</td>
<td>Hexagonal, honeycomb appearance with no or mild increase in the number of capillaries</td>
<td>Star-shaped luminal crypt openings or focal aggregation of regularly shaped crypts with a regular or reduced amount of goblet cells</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>Dilated and distorted vessels; irregular architecture with little or no orientation to adjunct tissue</td>
<td>Ridged-lined irregular epithelial layer with loss of crypts and goblet cells; irregular cell architecture with little or no mucin</td>
</tr>
</tbody>
</table>

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Fig. 9 Colon and esophagus seen with confocal laser endomicroscopy (CLE). a Normal colonic mucosa; b hyperplastic colonic polyp; c colonic adenoma; d colorectal carcinoma; (for specific features see Mainz classification, Table 7). e, f Barrett’s esophagus: e surface view with visible goblet cells; f deeper layers showing lamina propria (bright) and epithelial cells (dark bands)
The big disadvantage of the current pilot computer algorithms is that they require manual segmentation of lesions before the algorithm can attempt a classification. In other words, the boundary of the lesion in the image must first be delineated by a human operator. Emerging work attempts to improve that aspect of CAD [72]. How such systems will be deployed in clinical practice remains unclear, with a number of possible paradigms. The most likely scenario is that these systems will be used as a “second reader” to support the endoscopist’s diagnosis, with the endoscopist making the final decision or only making a definite high confidence assessment when endoscopist and CAD system agree. The “stand alone” use of such systems to completely replace clinical judgment for decision making would require a much higher diagnostic performance and additional safeguards. Nevertheless availability of CAD combined with advanced endoscopic imaging is likely to emerge in clinical practice in the next few years.

6.5 Techniques and utility of advanced endoscopic imaging in clinical practice (Table 9)

### 6.1 Esophagus

**Heterotopic gastric mucosa.** In an observational cohort study the routine use of NBI was shown to improve detection of inlet patches threefold compared to white-light endoscopy (WLE) (3% vs. 1%, P=0.005) [73].

**Squamous Neoplasia.** In a randomized study NBI was shown to double the detection rate of squamous cell carcinoma and of high grade dysplasia in the esophagus [74]. NBI with magnification is also helpful to determine the likely invasiveness of lesions, using the IPCL (Inoue) classification [24]. FICE (Fig.7c) was similar to Lugol chromoendoscopy for detecting early squamous cell carcinoma (93% vs 89%, P>0.05) [75]. AFI had a higher sensitivity than WLE in detecting superficial lesions (79% vs. 51%) [76]; however, its ease of detection for squamous cell carcinoma was lower than that of Lugol chromoendoscopy or NBI in a small study based on still images [77]. ICLE showed good diagnostic performance in a study of 43 lesions in 21 patients with early squamous cell carcinoma, with a sensitivity of 100% and a specificity of 87% [78]. pCLE also showed good accuracy in a small study of 21 Lugol-voiding (not stained by iodine) lesions, with a negative predictive value that was similar to that of near-focus NBI (92% vs. 89%) [79].

*Neoplasia in Barrett’s esophagus.* NBI was shown to present reasonable accuracy (75%) for the diagnosis of neoplasia in Barrett’s esophagus, independently of the classification system used (Kansas, Nottingham, or Amsterdam) [30]. The more recent BING classification system for NBI allowed an accuracy of 85%, which increased to 92% with high confidence predictions (Fig.2) [31]. I-SCAN has been shown in a small study to perform as well as acetic acid for targeting SIM, compared to random biopsy sampling (66% vs. 21% for I-SCAN-targeted vs. random biopsies, respectively) [80]. For the detection of neoplasia in Barrett’s esophagus, FICE allowed a per-lesion sensitivity of 87%, equivalent to that reported with acetic acid, in a study that involved 57 patients [81]. In a study that combined 5 study databases including 211 patients, AFI (Fig.8) yielded an incremental neoplastic diagnosis of 13% compared to WLE or random biopsies [82]. In a meta-analysis of iCLE and pCLE (Fig.9) that included 7 studies with 473 patients, pooled per-patient sensitivity and specificity were 89% and 83%, respectively [83].

**Gastroesophageal reflux disease (GERD).** At NBI, patients with GERD showed increased number, and dilatation, and tortuosity of IPCls, and greater presence of microerosions compared to controls (P<0.001) [84]. Interobserver and intraobserver reproducibility also was improved with NBI, because of better depiction of small erosive foci [85]. I-SCAN showed significantly improved diagnosis of reflux esophagitis (Fig.6c) compared to WLE (30% vs. 22%, respectively), as well as improved detection of minimal reflux changes (12% vs. 6%, respectively) [86]. For detecting GERD in 82 patients, AFI showed higher sensitivity and accuracy compared to WLE (77% and 67% vs. 21% and 52%, respectively), but lower specificity (53% vs. 97%) [87].

**Eosinophilic esophagitis.** The recognition of eosinophilic esophagitis was not improved with NBI [88] but specific changes have been described with CLE in a case report [89].

### 6.2 Stomach

**Intestinal metaplasia.** For NBI, a meta-analysis of 4 studies reported sensitivity and specificity for intestinal metaplasia of 86% and 77%, respectively [90]. The “light blue crest sign” seen with magnification-NBI (Fig.3, Video 1) had sensitivity and specificity of 89% and 93%, respectively [32]. The yield of FICE endoscopy was assessed by comparing random and selective biopsy samples in 126 consecutive patients. For diagnosis of high risk intestinal metaplasia, sensitivity, specificity, and accuracy were 71%, 87%, and 86% respectively [91]. AFI followed by NBI (Fig.3, Video 1) detected more patients with intestinal metaplasia than did WLE (26/38 vs.

---

### Table 8 Diagnostic performance of computer algorithms for colonic polyp diagnosis.

<table>
<thead>
<tr>
<th>First author, year, reference</th>
<th>Method</th>
<th>n</th>
<th>Size</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Accuracy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varnavas 2009 [71]</td>
<td>NBI magnification</td>
<td>62</td>
<td>–</td>
<td>82</td>
<td>79</td>
<td>81</td>
</tr>
<tr>
<td>Tischendorf 2010 [66]</td>
<td>NBI magnification</td>
<td>209</td>
<td>–</td>
<td>94</td>
<td>93</td>
<td>86</td>
</tr>
<tr>
<td>Hafner 2012 [69]</td>
<td>Chromoendoscopy magnification</td>
<td>716</td>
<td>–</td>
<td>77</td>
<td>89</td>
<td>86</td>
</tr>
<tr>
<td>Takeamura 2012 [70]</td>
<td>NBI magnification</td>
<td>371</td>
<td>–</td>
<td>98</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>Gross 2012 [68]</td>
<td>NBI magnification</td>
<td>434</td>
<td>≤10mm</td>
<td>95</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td>Andre 2012 [67]</td>
<td>pCLE</td>
<td>135</td>
<td>1–60mm</td>
<td>93</td>
<td>83</td>
<td>90</td>
</tr>
</tbody>
</table>

NBI, narrow band imaging; pCLE, probe-based confocal laser endomicroscopy.
13/38, \( P=0.011 \), in a prospective, randomized crossover trial that included 65 patients [92]. CLE consistently outperformed WLE in the detection of intestinal metaplasia and its diagnostic performance is similar to that of magnification-NBI [93]. However in a parallel group randomized controlled trial of CLE vs. WLE in 168 patients for the diagnosis of intestinal metaplasia, the difference in rates was not significant on a per-patient basis (45% and 31%, respectively, \( P=0.074 \)) [94].

**Gastric dysplasia.** For the diagnosis of dysplasia in the stomach with NBI (Fig. 3, Video 1), a meta-analysis of 4 studies reported sensitivity and specificity of 90% and 83%, respectively [90].

In another study, magnified I-SCAN was shown to have sensitivity and specificity for high grade dysplasia (HGD) and cancer versus all other diagnoses (including intestinal metaplasia and low grade dysplasia) of 100% and 77%, respectively [95]. Magnified FICE also yielded an increased agreement between endoscopic and pathological diagnosis compared with WLE [96]. AF alone did not improve diagnosis of superficial gastric neoplasia on a per-lesion basis compared to WLE, with sensitivity of 68% vs. 77%, and specificity of 24% vs. 84%, respectively [97].

In a large study that included 1786 patients, iCLE was significantly more accurate than WLE for the diagnosis of high grade dysplasia and early gastric cancer (99% vs. 94%, respectively) [98].

**Helicobacter pylori (H. pylori) diagnosis.** Variable vascular density in the gastric mucosa seen with NBI was moderately associated with \( H. \) pylori infection with an overall accuracy of 70%. In a pilot study, I-SCAN with magnification outperformed magnifying WLE for the prediction of \( H. \) pylori infection with accuracy of 94% versus 85% (\( P=0.046 \)) [99]. A case report described how iCLE in the stomach allowed direct in vivo visualization of \( H. \) pylori [100]. A further blinded, prospective study involving 83 patients where iCLE was used for \( H. \) pylori diagnosis demonstrated an accuracy of 93% [101].

### 6.3 Duodenum

**Villous atrophy.** For detecting villous atrophy associated with celiac disease, FICE (accuracy 100%) and NBI (sensitivity 93%, specificity 98%) both seem helpful [102]. CLE also showed excellent diagnostic performance compared to histopathology in a study of 31 patients with a receiver operating characteristic area under the curve of 0.946 [103]. I-SCAN was shown to allow excellent accuracy for the diagnosis of total villous atrophy (100%) but performed less well in assessing partial villous atrophy or normal villi (90% each) [104].

**Familial adenomatous polyposis.** In 33 patients with familial adenomatous polyposis, NBI did not lead to a clinically relevant upgrade in the Spigelman classification of duodenal polyposis and it did not improve the detection of gastric polyps in comparison with WLE. However more duodenal adenomas were detected with NBI in 16 examinations [105].

**Ampullary dysplasia.** When the duodenal ampulla was assessed for dysplasia, the observation with NBI of pinecone- or leaf-shaped villi or irregular/nonstructured villi accurately predicted dysplastic changes in a small study (14 patients) [106]. A pilot study (12 lesions) to evaluate the utility of pCLE for ampullary lesion assessment showed poor interobserver agreement [107].

### 6.4 Small intestine

**Vascular lesions found at capsule endoscopy.** In a study of 152 vascular lesions detected by capsule endoscopy in the small intestine, FICE enhancement was considered to improve color contrast and

---

**Table 9** Utility of advanced endoscopic imaging techniques throughout the gastrointestinal tract. Clinical utility which represents both evidence and likely clinical impact: +++, very useful; +, useful; +/-, indeterminate; –, no additional benefit. References cited in the left-hand column indicate major reviews of the literature or meta-analysis; otherwise key references shown.

<table>
<thead>
<tr>
<th>Technique</th>
<th>NBI</th>
<th>I-SCAN</th>
<th>FICE</th>
<th>AF</th>
<th>CLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Esophagus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inlet patch</td>
<td>+ [73]</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Squamous cell carcinoma (SCC) esophagus</td>
<td>+/+ [24, 74]</td>
<td>NA</td>
<td>+ [75]</td>
<td>+/- [76, 77]</td>
<td>+/- [78, 89]</td>
</tr>
<tr>
<td>Barrett’s esophagus</td>
<td>+ [30]</td>
<td>+/- [80]</td>
<td>+ [81]</td>
<td>+/- [82]</td>
<td>+/- [83]</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>+ [84, 75]</td>
<td>+ [86]</td>
<td>NA</td>
<td>+/- [87]</td>
<td>NA</td>
</tr>
<tr>
<td>Eosinophilic esophagitis</td>
<td>– [88]</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>+/- [89]</td>
</tr>
<tr>
<td><strong>Stomach</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>+/+ [32, 90]</td>
<td>NA</td>
<td>+/- [91]</td>
<td>+ [92]</td>
<td>+/+ [93, 94]</td>
</tr>
<tr>
<td>Early gastric cancer (diagnosis)</td>
<td>+/ [33, 90]</td>
<td>+/- [95]</td>
<td>+/- [96]</td>
<td>– [97]</td>
<td>+ [98]</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>+/- [33]</td>
<td>+/- [99]</td>
<td>NA</td>
<td>NA</td>
<td>+ [100, 101]</td>
</tr>
<tr>
<td><strong>Duodenum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celiac disease [102]</td>
<td>+</td>
<td>+/ [104]</td>
<td>+</td>
<td>NA</td>
<td>+/+ [103]</td>
</tr>
<tr>
<td>Familial adenomatous polyposis (FAP) / Polyposis</td>
<td>– [105]</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ampulla dysplasia</td>
<td>+ [106]</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>– [107]</td>
</tr>
<tr>
<td><strong>Small intestine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiodysplasia</td>
<td>NA</td>
<td>NA</td>
<td>+/ [108, 109]</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Colorectum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyp assessment “optical biopsy” [110]</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Sporadic polyp detection [112]</td>
<td>–</td>
<td>+/</td>
<td>–</td>
<td>+/</td>
<td>NA</td>
</tr>
<tr>
<td>Colitis surveillance (detection)</td>
<td>– [113]</td>
<td>NA</td>
<td>NA</td>
<td>+/- [115]</td>
<td>NA</td>
</tr>
<tr>
<td>Microscopic colitis</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>+ [117, 118]</td>
</tr>
<tr>
<td>IBD mucosal healing</td>
<td>+/- [119]</td>
<td>+/ [120]</td>
<td>NA</td>
<td>NA</td>
<td>+/- [121, 122]</td>
</tr>
</tbody>
</table>

NBI, narrow band imaging; I-SCAN, i-Scan digital contrast; FICE, flexible spectral imaging color enhancement; AF, autofluorescence imaging; CLE, confocal laser endoscopy; NA, no data available.
allowed a higher sensitivity than WLE (100% vs. 83%, respectively) [108]. However in a study of 60 patients there was no difference in detection of vascular lesions assessed as pathological at capsule endoscopy using FICE compared to WLE, with more non-pathological lesions detected by FICE (39 vs. 8, P<0.001) [109].

6.5 Colon

Polyph characterization and detection. A meta-analysis that summarized a total of 91 studies looking at the ability to characterize polyps as adenomatous or hyperplastic, using NBI, FICE, I-SCAN, AFI, or CLE (Fig. 4, Fig. 5, Fig. 6, Fig. 7, Fig. 8, Fig. 9, Video 2), concluded that all techniques except AFI (sensitivity 87%, specificity 66%) could be used by appropriately trained endoscopists to make an optical diagnosis [110]. The ESGE Guideline on advanced imaging in the colorectum supports the clinical use of NBI, FICE, and I-SCAN for optical diagnosis of diminutive (≤5mm) polyps by experts [4]. The American Society for Gastrointestinal Endoscopy offers similar support but for NBI only [111]. For the detection of sporadic polyps in average-risk individuals a summary of 6 meta-analyses (range 5–14 studies, 1199–5074 patients) that considered NBI, FICE, I-SCAN, and AFI, did not show a significant benefit for adenoma or polyp detection for any modality [112]. The ESGE Guideline on advanced imaging in the colorectum did not support the clinical use of NBI, FICE, or I-SCAN to enhance polyp detection [4].

Inflammatory bowel disease (IBD). For colonoscopic surveillance of longstanding IBD to detect dysplasia, chromoendoscopy is now the recommended standard of care in international guidelines [4, 113, 114]. NBI was not shown to be significantly superior to chromoendoscopy in a meta-analysis conducted for an international consensus statement on surveillance and management of dysplasia in IBD which favored chromoendoscopy (incremental yield, 6%; 95% confidence interval –1 to 14%) [113]. A single-center back-to-back study comparing AFI and WLE in 50 patients showed a lower miss rate with AFI (0/10 vs. 3/6; P=0.036) [115]. No head-to-head comparison with chromoendoscopy is available. The ESGE Guideline did not support narrowed-spectrum endoscopy or AFI as an alternative to chromoendoscopy in colitis surveillance [4].

Microscopic colitis, both collagenous and lymphocytic, has been shown to be detectable with iCLE, in case reports and small case series [116–118]. Whether this translates into true clinical utility remains to be defined.

Mucosal healing in IBD is now recognized as an important outcome and apparently normal “healed” mucosa can be subclassified using advanced endoscopic imaging techniques, recognized in recent guidelines from the European Crohn's and Colitis Organisation (ECCO) [114]. NBI has allowed detection of increased angiogenesis in IBD mucosa that looked normal using WLE [119]. Retrospective assessment of I-SCAN images in 78 consecutive patients with ulcerative colitis showed subtle vascular and mucosal abnormalities in patients with Mayo endoscopy subscore of 0 or 1 at WLE, and these abnormalities closely related to histological outcomes [120]. Local barrier dysfunction of normal mucosa (cell shedding, fluorescein leakage), demonstrated by CLE, predicted relapse in IBD at 12 months [121]. Healed mucosa in ulcerative colitis showed impaired crypt regeneration, persistent inflammation, and abnormalities in angioarchitecture and increased vascular permeability under CLE examination [122].

7. Conclusion and future research questions (Box 1)

Advanced endoscopic imaging has become a routine part of the practice of most endoscopists; however to realize the benefits from these technologies we need robust evidence as to their effectiveness. The second challenge is then translating this into real world changes that benefit patients. Although in the last decade considerable advances have been made in demonstrating effectiveness [4], especially in academic centers, the quality and quantity of data to allow widespread adoption in community-based practice is either lacking or has been disappointing. The use of narrowed-spectrum endoscopy for optical diagnosis of diminutive colon polyps is a case in point, where early expectations of high diagnostic accuracy with a short learning curve have been tempered by experiences in community-based studies where diagnostic performance has not met criteria for safe introduction to community-based practice [58, 59, 110, 123]. However recent data suggest that by changing the way we introduce new advanced imaging techniques, with periodic training, audits, and feedback, we may be able to convert promising early results into safe, widespread community implementation [124, 125]. These concepts need to be included into training programs for endoscopists.

We therefore need to plan studies on new techniques that move rapidly beyond single-center, single-operator studies towards the larger, more controlled studies, in large numbers of patients that we see in other medical specialties, notably oncology and cardiology. The development of validated criteria or scales for diagnosis by advanced endoscopic imaging, and of defined training programs to help endoscopists surmount the learning curves for use of these technologies, linked to outcomes, will be a key area of research for the endoscopic community [126].
ESGE technology reviews represent a consensus of best practice based on the available evidence at the time of preparation. They are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment.

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**Institutions**

1. Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford, United Kingdom
2. Department of Gastroenterology and Hepatology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands.
3. Gastroenterology Department, University Hospital Leuven, Leuven, Belgium
4. Solent Centre for Digestive Diseases, Queen Alexandra Hospital, Portsmouth, United Kingdom
5. Endoscopy Unit, Nuovo Regina Margherita Hospital, Rome, Italy
6. Centre for Colorectal Disease, St. Vincent’s University Hospital, Elm Park, Dublin, Ireland
8. Wolfson Unit for Endoscopy, St. Mark’s Hospital, London, United Kingdom
9. Gdyt Endoscopy Center, Buenos Aires, Argentina

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