

**Advances in CRC prevention: screening and surveillance**

Running title: "Enhancing detection and resection in colonoscopy"

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Email: [e.dekker@amc.uva.nl](mailto:e.dekker@amc.uva.nl)**Disclosures:** ED received research equipment on loan and unrestricted research grants from Olympus and FujiFilm, and a consulting fee from FujiFilm. DKR is a consultant for Olympus and Boston Scientific and receives research support from Boston Scientific, Endochoice, EndoAid and Medtronic.**Word count:****References:****Keywords:** colorectal cancer, screening, colonoscopy**Acknowledgements:** The authors thank Jasper Vleugels, research fellow at the Department of Gastroenterology & Hepatology at the Academic Medical Center, Amsterdam, the Netherlands, for his invaluable help in preparing this manuscript.

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1 **ABSTRACT**

2 Colorectal cancer (CRC) is amongst the most commonly diagnosed cancers and causes of death from  
3 cancer across the world. CRC can, however, be detected in asymptomatic patients at a curable stage,  
4 and several studies have shown lower mortality among patients who undergo screening compared to  
5 those who do not. Using colonoscopy in CRC screening also results in the detection of precancerous  
6 polyps that can be directly removed during the procedure, thereby reducing the incidence of cancer.  
7 In the past decade, convincing evidence has appeared that the effectiveness of colonoscopy as CRC  
8 prevention tool is associated with the quality of the procedure. This review aims to provide an up-to-  
9 date overview of recent efforts to improve colonoscopy effectiveness of by enhancing detection and  
10 improving the completeness and safety of resection of colorectal lesions.

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## 1 INTRODUCTION

2           Approximately 50 years after the introduction of diagnostic colonoscopy and polypectomy<sup>1,2</sup>,  
3 colonoscopy is firmly entrenched across much of the world as one of the most commonly performed  
4 and valuable procedures in clinical medicine. In many countries, colonoscopy is the primary imaging  
5 test to evaluate patients with colorectal symptoms, particularly those with bleeding. Colorectal  
6 bleeding in its various forms, including hematochezia, iron deficiency anemia, melena with a negative  
7 upper endoscopy, and positive fecal blood test, has a substantially higher predictive value for  
8 colorectal cancer (CRC) compared to colonoscopy in patients with non-bleeding symptoms or no  
9 symptoms<sup>3,4</sup>. Excellent detection as well as same session biopsy and potentially also treatment have  
10 made colonoscopy the test of choice in bleeding patients.

11           In addition to prevention of colorectal cancer deaths through detection of curable cancers,  
12 colonoscopy can also prevent most incident cancers. As CRC develops gradually from premalignant  
13 adenomatous and serrated polyps, colonoscopy with polypectomy provides an opportunity to halt  
14 this process. Evidence for cancer prevention by colonoscopy is found in a randomized controlled trial  
15 of fecal blood testing<sup>5</sup>, a surveillance study<sup>6</sup>, cohort<sup>7</sup> and case control studies<sup>8-10</sup>, and in large trials  
16 evaluating variable detection<sup>11,12</sup>. CRC prevention via colonoscopy is achieved through effective  
17 detection and resection of precancerous lesions. No other available imaging technique matches or  
18 even approaches the sensitivity of colonoscopy for precancerous lesions, particularly for serrated  
19 polyps<sup>13</sup>.

20           Despite its strengths, colonoscopy has certain disadvantages and limitations. Colonoscopy  
21 has a relatively long learning curve, and fully trained colonoscopists demonstrate marked variation in  
22 polyp detection<sup>14,15</sup>, cancer prevention<sup>11,12</sup>, polyp resection<sup>16</sup>, and use of appropriate screening and  
23 surveillance intervals<sup>17</sup>. Colonoscopy carries risks associated with bowel preparation, sedation,  
24 aspiration, perforation, and splenic injury. Patients subjected to resection of all exposed lesions  
25 sometimes suffer post-polypectomy hemorrhage, including from lesions with an extremely low risk  
26 of ever causing harm, and which would not have been detected by other imaging or screening  
27 modalities.

28           Delivering high quality colonoscopies should be the aim of all endoscopists. In this review we  
29 summarize ongoing efforts to improve the quality of colonoscopy as a detection and resection tool,  
30 as well as efforts to improve its safety and cost-effectiveness.

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## 32 QUALITY IN COLONOSCOPY

1 Colonoscopy is currently regarded as the reference standard to detect and prevent CRC. It is  
2 widely practiced and generally safe and accurate, but not perfect. In the past decade, worldwide  
3 awareness on the importance of quality assurance of colonoscopy has emerged. Tandem  
4 colonoscopy studies, in which patients undergo colonoscopy twice in the same day, provided the first  
5 direct evidence that colonoscopy systematically misses small colorectal polyps, and some larger  
6 polyps<sup>18, 19</sup>. Further, there was evidence that some endoscopists missed more polyps than others,  
7 and this variable detection was shortly associated with examination technique during withdrawal<sup>20</sup>.  
8 An audit study in 2003 in the UK identified a remarkably low adjusted cecal intubation rate of only  
9 56.9%, demonstrating that in some countries poor performance extended to insertion technique and  
10 the ability to achieve complete examinations<sup>21</sup>. These findings were the origins of widespread efforts  
11 to improve colonoscopy performance and reduce operator dependence in basic colonoscopy  
12 outcomes. Subsequently, a vast amount of research on quality and accuracy of this procedure has  
13 appeared in literature.

14 Regarding detection, colonoscopy is not fully protective for the development of post-  
15 colonoscopy CRCs, which are disproportionately located in the right-sided colon<sup>8, 22-26</sup>. Post-  
16 colonoscopy (interval) CRCs are defined as CRCs diagnosed after a complete negative or clearing  
17 colonoscopy and diagnosed before the recommended surveillance or screening interval<sup>27</sup>. The  
18 majority of those post-colonoscopy cancers appears to be the result of procedural related factors  
19 and not related to patient- or biological factors<sup>27</sup>. This is supported by a study reporting that 23% of  
20 patients with a newly diagnosed CRC larger than 2 cm had undergone a colonoscopy within the  
21 preceding 30 months<sup>28</sup>. Certainly to achieve optimal effectiveness of this invasive procedure, the  
22 procedure should have proper indications, the interval between surveillance intervals should be  
23 consistent with guideline recommendations, and the benefits of the procedure should outweigh the  
24 complication risk, burden and other disadvantages of an invasive procedure.

25 In an effort to assess the quality of colonoscopy between endoscopists and practices, various  
26 quality indicators have been proposed in guidelines<sup>29-32</sup>. Ideally such indicators are based upon clear  
27 evidence, and for several parameters such evidence is available. For each phase of the colonoscopy,  
28 i.e. preprocedure, intraprocedure and postprocedure, registration of quality indicators is  
29 recommended (TABLE A)<sup>29</sup>.

30 A colonoscopy is only complete and accurate if the whole colon, including the cecum, is  
31 visualized. Low cecal intubation rates (CIRs) have been associated with higher rates of proximal post-  
32 colonoscopy cancers<sup>33</sup>. Therefore, cecal intubation should be confirmed and photodocumented by  
33 endoscopic pictures of the cecal landmarks, ileocecal valve and appendiceal orifice. Effective

1 endoscopists should achieve cecal intubation rates of at least 90%, and when adjusted for strictures,  
2 stenosis and poor bowel preparation or in healthy adults with an indication of screening at least 95%  
3 <sup>29-32</sup>.

4 To ensure safe intubation and optimal inspection, adequate bowel preparation is  
5 indispensable. Poor bowel cleansing has been associated with incomplete colonoscopy, prolonged  
6 procedure time and reduced yield. Studies demonstrating the correlation between bowel prep  
7 quality and post-colonoscopy CRCs are, however, not available yet<sup>31</sup>. Assessment of the quality of the  
8 bowel preparation is essential and should be documented with a validated scale, for example the  
9 Boston Bowel Preparation Score (BBPS)<sup>34</sup>. This score is used after optimal cleaning and rinsing, and  
10 thus a judgment of the final situation at which inspection took place. BBPS scores of  $\geq 2$  in each of  
11 three colon segments correlated with adequate bowel cleansing<sup>35</sup>, and should allow the  
12 colonoscopist to recommend a screening or surveillance interval appropriate to the findings of the  
13 examination, without the need to shorten the recommended interval based on preparation quality.  
14 Consistent with this conclusion, segmental scores of  $\geq 2$  predict a lower risk of polyps in that segment  
15 at follow up colonoscopy<sup>36</sup>.

16 The bowel-cleansing regimen is regarded as burdensome by many patients. The optimal  
17 bowel preparation is effective, tolerable and safe, also for individuals with comorbidities. Multiple  
18 regimens exist, which can be roughly divided into high and low volume preparations. The high  
19 volume preparations are the 4 liter polyethylene glycol -electrolyte lavage solutions (PEG-ELS), which  
20 are suitable for all patients and which, when given in split doses, are likely the gold standard for  
21 effectiveness. 4 L PEG-ELS causes less fluid and electrolyte shifts than hyperosmotic preparations,  
22 and are often preferred for patients with renal insufficiency, heart failure, and decompensated liver  
23 disease. Because of their high level of effectiveness, 4L PEG-ELS preparations are preferred in many  
24 units for patients with clinical features that predict difficulty achieving adequate preparation,  
25 including those with chronic constipation, obesity, diabetes mellitus, and those on opioids or  
26 tricyclics. Patients with a history of ineffective preparation are often given >4L of PEG-ELS.  
27 Conversely, high volume is often difficult to tolerate and some patients cannot complete ingestion.  
28 For many healthy outpatients, low volume preparations provide high quality preparation and  
29 improved tolerance. Hyperosmotic, low volume preparations based on sodium phosphate or sodium  
30 sulfate are effective, though rare instances of renal failure from sodium phosphate have markedly  
31 reduced its use in the U.S.. Other low volume preparations include combinations of 2L PEG-ELS plus  
32 ascorbate, and in the U.S there is substantial use of non-FDA approved regimens based on PEG3350  
33 in sport drinks, or on magnesium citrate, or combinations of these agents. Other low volume  
34 preparations include combinations of 2L PEG-ELS plus ascorbate as well as "home-made"

1 preparations based on PEG3350 in sport drinks, which is often combined with magnesium citrate.  
2 Split-dosing, i.e. giving half the regimen the evening before colonoscopy and half on the morning of  
3 colonoscopy, improves bowel prep quality and detection compared to evening before regimens.  
4 “Same-day” dosing, in which the entire preparation is given the morning of colonoscopy, is also  
5 effective. The US Multi-Society Task Force recommended that colonoscopy programs should be able  
6 to achieve adequate bowel preparation in at least 85% of outpatient examinations<sup>37</sup>. This document  
7 as well as the European guideline can be consulted for best practice<sup>37,38</sup>.

8 Thorough inspection of the colonic mucosa is crucial to optimize its effectiveness. Most  
9 mucosal inspection takes place during withdrawal of the endoscope from cecum to rectum. Taking at  
10 least 6 or more minutes to inspect the colonic mucosa is associated with an increase in adenoma  
11 detection rate (ADR).<sup>14</sup> The ADR is currently considered one of the most important evidence-based  
12 quality indicators for colonoscopy. Two landmark papers have demonstrated that the ADR of  
13 individual endoscopists is associated with the risk of post-colonoscopy CRCs<sup>11,12</sup>. Patients scoped by  
14 a colonoscopist with an ADR of <20% had a 10 times higher risk for post-colonoscopy cancer than  
15 when scoped by an endoscopist with an ADR >20%<sup>11,12</sup>. Most guidelines recommend an ADR of at  
16 least 20-25% in screening colonoscopies. Although a clear evidence-based quality indicator, ADR also  
17 has some inherent limitations. First, the target ADR depends on the population scoped. When  
18 colonoscopy is used as a primary screening method, average ADR is expected to be relatively low but  
19 above 20-25%<sup>29-32</sup>, whereas ADRs in FIT-positive screenees have a much higher median of at least  
20 around 50%<sup>39,40</sup>. Other risk factors like patients’ sex also heavily influence target ADRs<sup>41</sup>. Besides,  
21 the ADR does not evaluate the total number of adenomas per individual patient, which is especially  
22 important in populations with high ADRs like FIT-positive screenees. To measure ADR, the  
23 histopathology result must often be manually derived from a pathology database, making it a more  
24 complicated parameter for monitoring purposes. However, while conventional adenomas are the  
25 clear precursors of the majority of colorectal cancers, some serrated lesions (sessile serrated lesions  
26 and traditional serrated adenomas) are precursors for CRC and should also be detected and  
27 removed. Those serrated polyps are not included in ADRs. A few recent studies suggested the  
28 proximal serrated polyp detection rate as quality parameter for high quality colonoscopy, however  
29 the association between a serrated polyp detection rate and post-colonoscopy CRCs has yet to be  
30 determined<sup>42,43</sup>. Further, differentiation of hyperplastic polyps (which are generally considered to  
31 not be precancerous) from sessile serrated lesions is still generally subject to large interobserver  
32 variation in pathology interpretation<sup>44</sup>, which complicates developing an endoscopic quality target  
33 for detection of sessile serrated lesions.

1            Resection is an emerging area for quality measurement. A single center study found that  
2 effective eradication of polyps 5-20 mm in size varied 3 fold between endoscopists<sup>16</sup>. A tool  
3 developed and validated in Europe to assess polypectomy competency (The Direct Observation of  
4 Polypectomy Skills or DOPyS)<sup>45</sup> was recently used to assess 13 high-volume screening colonoscopists  
5<sup>46</sup>. Among all polypectomies observed and scored blindly, only 64% were judged competent, and  
6 between endoscopists competent resections varied from 30% to 90% of polypectomies. Specific  
7 competencies that varied between endoscopists included achieving the optimal positioning of the  
8 polyp, determining the extent of the lesion, maintaining a stable endoscope position, accurately  
9 placing the snare, achieving an adequate margin of normal tissue, examining the resection site for  
10 residual polyp and removing residual polyp when present. Detection as measured by ADR and  
11 competency in polypectomy had little correlation. Thus, a validated tool is now available both for  
12 teaching polypectomy and assessing polypectomy competency.

13            Assessment of patient discomfort and complications of colonoscopy is also essential for  
14 quality assurance purposes. Use of carbon dioxide insufflation reduces post procedural pain and  
15 hospitalization for observation compared to room air insufflation<sup>47</sup>. Discomfort is also related to the  
16 depth of sedation, but deep sedation is associated with an increased risk for complications,  
17 particularly aspiration pneumonia<sup>48</sup>. The overall risk of complications after colonoscopy increases  
18 when individuals receive anesthesia services<sup>49</sup>. Sedation practice varies across centers, countries and  
19 continents and seems to be heavily influenced by expectations and beliefs of doctors and patients.  
20 For quality and auditing purposes, doses of sedatives and depth of sedation should also be reported  
21 and related to the comfort score. Recently, the composite performance indicator of colonic  
22 intubation (PICI), combining cecal intubation rate, comfort, and sedation was proposed<sup>50</sup>. Achieving  
23 PICI was significantly associated with the detection of one or more polyps, compared with  
24 procedures that did not achieve PICI.

25            The most ideal quality indicator for colonoscopy, however, is the rate of post-colonoscopy  
26 CRCs. To allow comparison, a clear definition on the taxonomy of interval cancers, including post-  
27 colonoscopy cancers, is of utmost importance and has been established<sup>27</sup>. However, whenever  
28 feasible, post-colonoscopy CRCs should be measured over a long time-span and enabled by accurate  
29 detection of those cancers. This requires large numbers of colonoscopy, structured reporting, and  
30 reliable coupling to a cancer registry. As post-colonoscopy CRCs are relatively rare, this parameter is  
31 less useful as a quality indicator for individual endoscopists, but should rather be used as an indicator  
32 at the level of a center or a national screening program.

1           These and other current quality indicators were gradually developed as new evidence  
2 emerged. Ongoing research will allow development of new indicators that are more accurate and  
3 comprehensive in their depiction of quality. Assessment and benchmarking of those quality  
4 indicators forms the basis for continuous quality improvement. Auditing and benchmarking, including  
5 provision of training to underperformers, demonstrated a benefit on CIR, ADR, post-colonoscopy  
6 CRCs and sedation-use<sup>51-53</sup>. To facilitate standardized and complete reporting on important quality  
7 indicators, structured terminology and colonoscopy reporting systems should be encouraged<sup>54-56</sup>.

## 9   **ADVANCED DETECTION TOOLS FOR COLORECTAL LESIONS**

10           From previous studies it is known that adenomas most prone to be missed at colonoscopy  
11 are small (<10 mm), flat and located at the proximal side of haustral folds or the inner curve of the  
12 hepatic or splenic flexure.<sup>24, 57, 58</sup> In a systematic review of tandem colonoscopy studies published  
13 between 1991 and 2004, a remarkable 22% pooled miss-rate for all polyps was reported<sup>57</sup>. The miss-  
14 rate for lesions measuring at least 1cm was 2%, for small polyps 13%, and for diminutive polyps 26%  
15<sup>57</sup>. In line with these results, a simulation study using CT-colonography estimated that 7.8% of the  
16 colonic surface is not visualized during standard colonoscopy using current wide-angle colonoscopies  
17 (170 degrees)<sup>59</sup>.

18           In the past years, high-definition white light endoscopy has become the standard of care for  
19 endoscopy, and guidelines advice their routine use<sup>29, 60, 61</sup>. Besides, several advanced technologies  
20 and devices have been developed aiming to improve polyp detection. These techniques include  
21 advanced imaging techniques as well as techniques that aim to increase visualisation of the colonic  
22 surface (FIGURE A). However, as discussed in the previous paragraph, ascertaining basic quality  
23 measures remains of paramount importance.

24           When assessing clinical studies on new endoscopic detection techniques, it is important to  
25 realize that blinding for the technique is impossible in these trials. Therefore, close attention should  
26 be given to the quality of such studies, and investigators should try to make the two modalities  
27 comparable in terms of patient population, quality of endoscopists, their experience with the new  
28 techniques as well as all basic quality indicators.

29           Most advanced imaging techniques are based on the principle that the mucosal structure of  
30 (pre-) malignant lesions differs from the surrounding healthy tissue and consequently differ in their  
31 ability to absorb and reflect light. This trait is then used to depict such lesions differently, thereby  
32 facilitating their detection. These techniques include virtual chromoendoscopy with narrow band



1 imaging (NBI), iScan, flexible spectral imaging color enhancement (FICE), blue laser imaging (BLI) and  
2 autofluorescence imaging (AFI). However, despite the plausibility of this approach and the early  
3 positive outcomes for these techniques as a detection-tool<sup>62-64</sup>, the pooled outcomes of these  
4 studies suggest that ADRs are not conclusively improved by the use of these imaging techniques<sup>60, 65,</sup>  
5<sup>66</sup>. It seems that when endoscopists become acquainted with this new technique and detect lesions  
6 they did not see before, this also affects their performance with (high-definition) white light  
7 endoscopy<sup>62, 67</sup>.

8 From CT-colonography studies it is known that especially adenomas located at the proximal  
9 side of haustral folds or the inner curve of the flexures are more prone to be overlooked at  
10 colonoscopy, as they lie outside the regular field of view of colonoscopy.<sup>68</sup> In order to increase  
11 visualisation of the colonic surface aiming to improve adenoma detection rates, several surface  
12 exposing technologies have been proposed. These surface exposing technologies include cap-fitted  
13 colonoscopy, Endocuff or EndoRings assisted colonoscopy, through-the-scope optical devices, full-  
14 spectrum endoscopy (FUSE) and (prototype) wide angle view colonoscopies. For these techniques,  
15 results on adenoma detection and miss rates have been variable between studies<sup>69-77</sup>. This is also  
16 true for the FUSE system: a first study showed large differences in miss rates<sup>71</sup>, but this positive  
17 result could not be confirmed in a subsequent large comparative randomized trial<sup>72</sup>. This example  
18 underlines the fact that large, randomized trials in daily practice are required to determine whether  
19 an improved ADR remains true in broader practices and whether the use of these endoscopes and  
20 devices is cost-effective and clinically warranted<sup>77</sup>.

21

## 22 CHARACTERIZATION OF LESIONS

23 For decision-making in the management of colorectal lesions, lesion characterization is  
24 crucial. First of all, the entire surface should be examined for factors associated with deep (>1000  
25 microns) submucosal invasion of cancer. These factors include morphologic features like ulceration,  
26 changes in the pit pattern, and disruption of the surface vessel pattern<sup>78</sup>. Often changes in the pits  
27 and vascular patterns that denote deep submucosal invasion are evident only in areas of surface  
28 ulceration. Deep submucosal invasion is associated with a higher risk of lymph node metastasis<sup>79, 80</sup>,  
29 and is generally a contraindication to both EMR and ESD. Such endoscopic features are generally  
30 specific for deep submucosal invasion (or even greater depth) but lack sensitivity for submucosal  
31 invasion generally<sup>81</sup>. Thus, the modern endoscopist should be familiar with other endoscopic  
32 features that are associated with an increased risk of submucosal invasion generally, though the  
33 depth of invasion may be superficial (<1000 microns). When superficial submucosal invasion is

1 present, endoscopic resection may be considered curative in some cases if it was performed en bloc.  
2 Thus, when these “other” endoscopic factors are present, en bloc resection by EMR or ESD is often  
3 preferred if feasible. These “other” factors associated with submucosal invasion generally include  
4 non-granular morphology (particularly if associated with depression), and the presence of a large  
5 nodule in an otherwise flat lesion (see below)<sup>81, 82</sup>. Recognition of deep submucosal invasion as well  
6 as other features associated with an increased risk of any invasion by non-expert endoscopists can  
7 be further improved, and training for endoscopic diagnosis for early invasive cancers is urgently  
8 needed to ensure optimal clinical practice for treatment of these lesions<sup>83</sup>. To systematically  
9 describe a lesion and assess the risk of deep as well as any submucosal invasion, several  
10 morphological classification systems have been developed. These include location, size, Paris  
11 classification, lateral spreading tumor classification (if applicable) and evaluation of the mucosal  
12 surface pattern with high-definition endoscopes and advanced imaging techniques<sup>84</sup> (FLOWCHART  
13 1).

14 The size of a lesion is directly related to the chance that the lesion harbors invasive growth  
15 into the submucosa. One to five mm (“diminutive”) lesions have a very low risk of invasiveness,  
16 whereas 6-9 mm (“small”) lesions have a tiny risk of 0 to 0.4%<sup>85</sup>. For lesions of 10mm and larger, the  
17 risk of cancer gradually increases from 2.4% for 10 to 20 mm lesions to a maximum of 19.4% for  
18 polyps measuring more than 20 mm in size<sup>86</sup>. However, measuring polyp size during colonoscopy is  
19 subject to inter-observer variability, and a gold standard is not available. A recent proof-of-concept  
20 simulation study using a visual grid cue during endoscopy to measure polyp-size showed promising  
21 results<sup>87</sup> and should be further explored. As long as objective tools for daily practice are not  
22 available, ideally an open snare or biopsy forceps with known size should be used to size a lesion  
23 before resecting it.

24 The Paris classification divides polyps into several categories depending on their morphology:  
25 pedunculated (0-1p), sessile (0-1s), slightly elevated (0-IIa), flat (0-IIb), slightly depressed (0-IIc) and  
26 excavated (0-III)<sup>88</sup>. Especially recognizing and classifying depressed and excavated morphology  
27 seems relevant. While rare, lesions of this specific morphology are associated with an increased risk  
28 of invasive growth. The term laterally spreading type (LST) lesion refers to lesions of at least 10mm<sup>89</sup>.  
29 For this type of lesions a separate classification is used, dividing these in granular and non-granular  
30 types. An increasing size, non-granular type LSTs and LSTs with a large dominant nodule >10mm in  
31 size are associated with an increased risk of harboring invasive growth<sup>81, 90-94</sup>.

32 The introduction of high-definition endoscopes allows for precise evaluation of mucosal  
33 surface patterns, the most helpful tool to predict histopathology of polyps. For colorectal lesions,

1 several surface pattern classification systems as the Kudo, NICE, WASP and JNET classification for  
2 both chromoendoscopy and virtual chromoendoscopy have been validated<sup>78, 95-100</sup>.

3 Besides assessment of submucosal invasion, accurate characterization could facilitate a  
4 “Resect and Discard” strategy, in which diminutive polyps are resected after endoscopic  
5 characterization but do not have to be submitted for histopathology. Diminutive polyps in the  
6 rectosigmoid endoscopically deemed to be hyperplastic (or at least serrated) at histopathology can  
7 be reasonably left in place<sup>101</sup>. Only about 2% of lesions deemed hyperplastic in the rectosigmoid are  
8 found to be sessile serrated lesions on histopathology<sup>102</sup>. In 2011, the American Society of  
9 Gastrointestinal Endoscopy published the so-called Preservation and Incorporation of Valuable  
10 Endoscopic Innovation (PIVI) guideline containing performance thresholds for this purpose<sup>101</sup>. For  
11 diminutive polyps that are diagnosed with high confidence, in combination with outcomes of  
12 histopathology assessment of larger polyps and those characterized with low confidence,  
13 endoscopists should achieve at least 90% agreement between surveillance intervals that he/she  
14 predicted by optical diagnosis and the definitive surveillance intervals that are based on  
15 histopathology. Besides, they should achieve at least 90% negative predictive value for neoplastic  
16 polyps in the rectum and sigmoid, i.e. at least 90% of polyps they assess as non-neoplastic are indeed  
17 not neoplastic at histopathology<sup>101</sup>. However, whereas expert endoscopists are able to achieve the  
18 PIVI-thresholds for diminutive polyps<sup>103-105</sup>, studies with endoscopists working in daily clinical  
19 practice have shown conflicting results<sup>106-111</sup>. This difference could be explained by differences in  
20 time and dedication, but also in training and feedback of performance. Recently, the UK national  
21 health policy has endorsed the Resect and Discard strategy for implementation in clinical practice<sup>112</sup>.  
22 For optimal cost-effectiveness however, studies evaluating the effect of validated training programs  
23 and regular feedback on PIVI-tresholds in daily practice are essential and underway. Other potential  
24 barriers for implementation of the strategy are acceptability by the public and potential medical-legal  
25 risk of Resect and Discard when the policy has been implemented and there is the inevitable  
26 occurrence of an interval cancer. In these instances the cause of the interval cancer will likely be a  
27 missed lesion nearby in the colon rather than a discarded diminutive lesion. The defense will depend  
28 on development of clear society and institutional policies and stored high-quality photographs of  
29 discarded lesions.

30

31 **RESECTION OF LESIONS**

1 The CARE study demonstrated that the problem of variable performance in colonoscopy also  
2 extends to polypectomy, identifying a threefold difference between endoscopists in rates of effective  
3 polyp resection<sup>16</sup>. Increasing polyp size and serrated histology also predicted ineffective resection<sup>16</sup>.

4 Polyps of all predicted histologic types and sizes identified proximal to the sigmoid colon are  
5 typically resected, though the wisdom of resecting diminutive polyps has recently been challenged  
6<sup>113</sup>. Despite the very low risk of cancer in diminutive lesions, available data on the natural history of  
7 small and diminutive polyps are in general confined to 2-3 years of observation<sup>85</sup>. These limited data,  
8 in combination with uncertainty about patient acceptance of leaving lesions in place for long  
9 intervals, means that resection of even diminutive lesions other than distal colon hyperplastic polyps  
10 is likely to remain standard for now.

11 Table B (TABLE B) shows several current and recent trends in endoscopic resection in the  
12 colorectum. Several resection techniques are currently available (FIGURE B). First, the use of hot  
13 forceps for removal of diminutive polyps has been largely abandoned, both because it is ineffective,  
14 leaving residual polyp in place in 17-53% of lesions<sup>114 115</sup> and because it creates thermal injury that is  
15 associated with unnecessary risk, especially of perforation. Animal studies show that thermal injury is  
16 much harder to control with hot forceps compared to snaring, even with optimal technique<sup>116</sup>.  
17 Further, guidelines stipulate that hot forceps should not be used for removal of lesions larger than 5  
18 mm<sup>117</sup>. Currently, the use of hot forceps in colonoscopy has been essentially reduced to the process  
19 of avulsion during EMR, in which flat areas (often associated with submucosal fibrosis) that are  
20 resistant to snaring, are removed with forceps (either hot or cold) rather than ablated<sup>118</sup>.

21 Second, the use of cold resection techniques rather than hot resection is increasing generally  
22 in polyp resection, primarily because it reduces risks. Cold resection has been found histologically to  
23 cause less injury to submucosal vessels compared to hot snaring<sup>119</sup>. In a randomized controlled trial  
24 comparing cold to hot snaring of small polyps in anticoagulated patients, cold snaring reduced the  
25 risk of delayed hemorrhage from 14% to 0%<sup>119</sup>. Similarly, conversion to cold snaring reduced the risk  
26 of delayed hemorrhage in an observational study performed in a single practice<sup>120</sup>. Several  
27 randomized controlled trials found that rates of complete polyp resection with cold snaring were not  
28 different from hot snaring<sup>121-123</sup>. One study found that resection of small polyps with a thin-wire stiff  
29 snare made specifically for cold snaring resulted in superior complete resection rates compared to a  
30 standard snare<sup>119</sup>, but results have been inconsistent<sup>124</sup>. Cold snaring is also considerably more  
31 time-efficient than hot snaring in some studies, reducing total procedure time by more than 5  
32 minutes<sup>125, 126</sup>. This is likely because there is no need to set up the cautery and patient grounding  
33 equipment before proceeding with resection. Cold snaring of larger lesions, or when mechanical

1 tension is needed for transection, commonly leaves a cord of white submucosal tissue protruding  
2 from the defect, but the cord is devoid of residual polyp and represents submucosal tissue <sup>127</sup>. The  
3 cold resection technique has been extended to lesions over 1 cm in size <sup>128</sup> and also to performance  
4 of endoscopic mucosal resection (EMR), particularly for serrated lesions, and it appears effective in  
5 initial studies <sup>129</sup> and is nearly devoid of complications. Additional data regarding effectiveness of  
6 cold EMR are needed.

7 A third trend is toward cold snare resection of diminutive and small lesions over cold forceps  
8 resection. When polyps reach a size of 4mm, snare resection is more effective and efficient  
9 compared to cold forceps methods <sup>130</sup>. Forceps methods are particularly inappropriate if piecemeal  
10 resection is required. A general rule that seems reasonable is that forceps resection of 1-3mm polyps  
11 is appropriate, particularly if it can be accomplished in one bite, and large capacity and jumbo  
12 forceps are more effective in this regard compared to standard forceps <sup>131</sup>.

13 A fourth trend is an increasing use of EMR over standard snare polypectomy techniques.  
14 EMR has emerged as the treatment as choice for nearly all flat and sessile lesions  $\geq$  20mm in size in  
15 the colorectum. A series of studies performed by multiple groups of expert endoscopists has  
16 delineated the effectiveness, safety, and superiority of EMR over surgical resection for lesions in this  
17 size group <sup>132-134</sup>. Modern EMR depends closely on advanced imaging and interpretation skills. In the  
18 absence of overt endoscopic evidence of deep submucosal invasion, morphologic features such as a  
19 nongranular surface, a large sessile component, and depression are predictors of submucosal of  
20 invasion <sup>81, 94</sup> that warrant *en bloc* resection when feasible, and appropriate handling of resected  
21 specimens by the endoscopist and pathologist. EMR is particularly important for serrated lesions,  
22 because submucosal injection of a contrast agent clearly delineates the lesion perimeter during  
23 piecemeal removal <sup>135, 136</sup>. The technique is considered appropriate for serrated lesions in the 10-  
24 20mm size range <sup>137</sup>. Inclusion of a contrast agent stains the submucosa so that any muscle injury is  
25 readily seen (as the target sign) leading to easy repair and prevention of delayed perforation <sup>138</sup>.  
26 Submucosal injection fluids that are more viscous than saline create superior submucosal cushions  
27 and improve the efficiency of resection <sup>139</sup>. Modern EMR emphasizes resection by snaring, with  
28 avulsion as a rescue method, rather than ablation of residual visible polyp tissue <sup>118</sup>. Cold resection or  
29 use of microprocessor controlled electrocautery with emphasis on cutting over coagulation current  
30 are increasingly utilized <sup>132</sup>. Some experts endorse performance of EMR under water and without  
31 submucosal injection. When the lumen is filled with water, the mucosa “floats” away from the  
32 muscularis propria, providing a margin of safety for resection in the submucosal plane without  
33 submucosal injection. Under water EMR allows *en bloc* resection of a larger group of lesions <sup>140</sup>,  
34 because submucosal injection typically increases lesion size. Potential disadvantages include difficulty

1 identifying muscle injury because of absence of submucosal staining, and peritoneal contamination if  
2 perforation occurs.

3 Endoscopic submucosal dissection (ESD) has advantages compared to EMR including a lower  
4 recurrence rate at first follow up. Also, a group of patients with superficial (SM1; upper one-third)  
5 submucosal invasion can avoid surgery compared to similar patients after piecemeal EMR <sup>141</sup>.  
6 Despite these advantages, the expansion of ESD in western countries is often delayed by low  
7 numbers of experienced practitioners, long learning curves for ESD, long procedure times, higher  
8 perforation rates compared to EMR, and lack of appropriate reimbursement. Advances in ESD  
9 technology, combined with the attractiveness of *en bloc* resection, are likely to increase the  
10 utilization of colorectal ESD in western countries over time. However, effective use of ESD depends  
11 on the appropriateness of the clinical indication <sup>142</sup>. An emerging area of resection that is receiving  
12 increasing attention and bypasses both EMR and ESD is the full thickness resection device <sup>143</sup>. This  
13 endoscopic technique has been developed to allow accurate diagnosis and potentially definitive  
14 treatment for lesions invading any depth of the submucosal layer of the colonic wall. It combines  
15 resection of the entire colonic wall performed after secure closure of the expected defect by the use  
16 of a modified over-the-scope-clip mounted on a cap with a preloaded snare.

17

## 18 **FUTURE TRENDS**

19 Table C (TABLE C) lists reasonable expectations for developments in colonoscopy relative to  
20 cancer prevention and cost-effectiveness of colonoscopy for neoplasia management. Several of the  
21 predicted developments constitute major paradigm shifts in colonoscopy application. However, given  
22 the steady advances in instrumentation, examination effectiveness, and polypectomy technique,  
23 reconsideration of fundamental approaches is appropriate and necessary.

24 There will be continued challenges to the role of colonoscopy as a primary screening  
25 strategy. New screening strategies based on risk stratification <sup>144</sup> may direct screening colonoscopy to  
26 the highest prevalence screening populations, while lower prevalence populations are screened with  
27 inexpensive, noninvasive, and highly specific tests like FIT. However, the challenges to achieving  
28 adherence to repetitive fecal screening outside of organized screening programs will make screening  
29 colonoscopy, with its potential for long term protection, continue to be an attractive screening  
30 approach in the opportunistic screening setting <sup>145</sup>. Continued progress in combined assays such as  
31 FIT-fecal DNA and other molecular markers can be expected to further displace screening  
32 colonoscopy, though for programmatic screening lower cost DNA tests are needed <sup>146, 147</sup>. As a

1 further development, these tests would ideally only detect those premalignant lesions that are close  
2 to developing into cancer. If this becomes reality, screening colonoscopies are likely to be replaced  
3 by therapeutic colonoscopies in those patients with relevant lesions at a truly high risk for CRC.

4 Second, there are potential consequences of the quality movement and the trend toward  
5 higher ADRs and the detection of increasing numbers of diminutive lesions. One consequence is that  
6 patients in the 60-70 year range with negative colonoscopies performed by high ADR colonoscopists  
7 would be reasonably expected to have a very low risk of ever developing CRC. Such patients might be  
8 advised to either stop screening or have only once or twice in a lifetime a screening colonoscopy.  
9 Second, for high ADR colonoscopists, the low-risk cohort of adenoma bearing patients will be  
10 expanded. For example, many 5-10 year examination intervals could be expected for 1-4 small  
11 tubular adenomas when the colonoscopies are performed by a high ADR examiner<sup>148</sup>. However, we  
12 expect that quality assurance, and consistent use of techniques and potentially also devices proven  
13 to enhance detection, will reduce the variation between high and low ADR examiners by time.

14 Also, the application of artificial intelligence (AI) technology will likely change polyp detection  
15 and differentiation practice. Detection programs will provide real-time assessment of the adequacy  
16 of colonoscope tip deflection and cleaning to expose all mucosa<sup>149</sup>, while simultaneously highlighting  
17 potential lesions. Strategies such as Resect and Discard, that eliminate the pathologic assessment of  
18 diminutive polyps or at least diminutive adenomas, are likely to emerge as accepted clinical  
19 strategies<sup>15</sup>. Previously hampered by poor performance among community endoscopists, the  
20 application of artificial intelligence (AI) technology to the prediction of colon polyp histologies will  
21 make strategies like Resect and Discard universally feasible. These achievements are likely to further  
22 reduce operator dependence in colonoscopy.

23 In the not-too-distant future, the combination of these trends may completely change the  
24 face of colonoscopy. Average-risk individuals participating in organized screening programs might be  
25 systematically invited to perform a highly selective stool-test at home. Those individuals with  
26 colorectal lesions at high-risk for CRC development will be invited to undergo a therapeutic  
27 colonoscopy, in which artificial intelligence will help with the detection of these lesions. After  
28 detection, polyp histology will be predicted, potentially followed by advice on the optimal resection  
29 technique and whether histopathological analysis is recommended. The endoscopist will perform en-  
30 bloc resection of the lesion using easier, less laborious, and safer techniques than those currently  
31 available. Finally, patient-selection for surveillance colonoscopies may also be based on the  
32 outcomes of stool-tests instead of risk-stratification at the time of the last colonoscopy.

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27 **FIGURE LEGENDS:**

28 Figure 1: Top: Proposed systematic approach for structured lesion description including  
29 morphological features associated with deep submucosal invasion.

30 Bottom: Schematic overview of several endoscopic resection methods.

31

32 Figure 2: Advanced imaging techniques. a; picture of a pT1sm2 adenocarcinoma using narrow band  
33 imaging, b; picture of a tubular adenoma with low-grade dysplasia using autofluorescence imaging, c;  
34 picture of a sessile serrated lesion without dysplasia using linked color imaging, d; picture of a tubular  
35 adenoma with low-grade dysplasia using blue light imaging.

**Table A.** Minimum recommended registration of preprocedure, intraprocedure and postprocedure quality indicators based on current prevailing international guidelines<sup>29-32</sup>.

Quality requirement	Description	Recommended minimum if applicable
<b>Preprocedure</b>		
Accreditation and professional registration	Accreditation conforming to the levels proposed by scientific society of gastroenterology and registration with a professional gastroenterology society	-
Number of colonoscopies	Number of (screening) colonoscopies performed per year	≥ 500 (lifetime)
Number of polypectomies	Number of polypectomies performed per year	≥ 50 (lifetime)
<b>Intraprocedure</b>		
<i>Completeness of exam</i>		
(Unadjusted) cecal intubation rate	The percentage of colonoscopies with a complete cecum intubation	≥ 90%
Bowel preparation	The percentage of colonoscopies where the colon is sufficiently clean to be able to inspect the mucosa well (BBPS ≥ 6)	≥ 90%
Withdrawal time	The percentage of negative colonoscopies with an withdrawal time	≥ 6 minutes
<i>Detection rates</i>		
Cancer detection rate	The percentage of colonoscopies where (more than) one cancer has been detected	-
Adenoma detection rate (ADR)	The percentage of colonoscopies where (more than) one adenoma has been detected	≥ 20%
MAP	The mean number of adenomas per procedure (colonoscopy)	-
PSPDR	The percentage of colonoscopies where (more than) one proximal serrated polyp has been detected	≥ 5%



<i>Removal rates</i>			
	Polyp removal rate	The percentage of polyps removed of the total number of detected polyps during the colonoscopy	≥ 90%
	Polyp retrieval rate	The percentage of retrieved polyps for histological evaluation of the total number of polyps detected during the colonoscopy	≥ 90%
<i>Tattoo placement</i>			
	Tattooing	The percentage of suspected cancers given a tattoo, except from cancers located in the cecum and up to 4 cm from the dentate line	100%
<i>Postprocedure</i>			
<i>Patient satisfaction</i>			
	Comfort Score	The percentage of colonoscopies in which the participant experiences moderate or severe discomfort (according to the GCS)	≤ 10%
<i>Wellbeing of patients</i>			
	Complication record	Keeping a complication record	-
	Complications during colonoscopy	The percentage of colonoscopies performed by the endoscopists where a complication occurs (up to 30 days after the procedure)	-
	Perforation rate colonoscopy	The perforation rate for colonoscopies performed by the endoscopist (up to 30 days after the procedure)	-
	Perforation rate polypectomy	The perforation rate for colonoscopies with polypectomy performed by the endoscopist (up to 30 days after the procedure)	-
	Polypectomy bleeding	The percentage of colonoscopies with polypectomy performed by the endoscopist , where complicated bleeding occurs (up to 30 days after the procedure)	-

**Table B.** Current and recent trends in polyp resection during colonoscopy.

1. Hot forceps are used only for avulsion of flat residual polyp that can't be snared during EMR; hot forceps have no advantage and result in unnecessary risk in the resection of diminutive polyps
2. Cold resection techniques continue to expand to an ever enlarging group of target lesions; including cold EMR
3. Cold snare resection is preferred over cold forceps resection even for diminutive lesions; snaring is more effective and efficient than forceps resection
4. The target set of lesions for EMR over standard polypectomy techniques continues to expand; for serrated lesions the threshold for performance of EMR should be 10-15 mm; all sessile and flat lesions $\geq 20$ mm should generally be treated by EMR rather than use of standard techniques
5. Several trends in the technical performance of EMR have emerged
a. Classification schemes based on morphology (e.g. Paris classification and non-granular vs granular) and blood vessel and pit classifications using image enhanced endoscopy allow prediction of cancer risk, appropriateness of endoscopic resection, and the need for en bloc resection
b. High definition instruments allow delineation of residual polyp during resection and at follow-up
c. Several viscous injection solutions perform better than saline
d. Contrast in the injection fluid defines lesion boundaries and stains the submucosa, permitting recognition of muscle injury
e. Microprocessor controlled currents emphasizing cutting over coagulation current reduce thermal injury and may reduce complications
f. Visible polyp that can't be snare resected should be avulsed with forceps rather than ablated

**Table C.** Predicted future trends in the use of colonoscopy for colorectal cancer detection and prevention

1. Screening colonoscopy in organized screening programs will be progressively reduced in low-risk persons by therapeutic colonoscopies, as inexpensive and highly-selective non-invasive fecal tests will identify patients with colorectal lesions at high-risk for CRC development
2. Patients with one or two negative colonoscopies after age 50 by high level detectors (high ADR endoscopists) will be recommended to forego further colorectal cancer screening based on minimal residual lifetime risk
3. The low risk adenoma bearing cohort recommended to undergo next examination in 5-10 years will, when examination is performed by high ADR colonoscopists, be expanded to include persons with 3-4 small or diminutive tubular adenomas with low-grade dysplasia
4. Operator dependence in colonoscopy performance will be progressively reduced by quality improvement programs and technical improvements
5. Artificial intelligence (deep learning) programs will provide real-time assessment of withdrawal technique, assistance in lesion identification, and prediction of histology

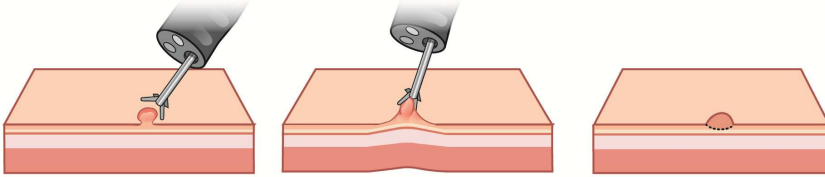
## Systematic lesion assessment

1. Record the location of the lesion
2. Size next to reference point of known diameter
3. Paris and LST classification
4. Surface pattern with high-definition electronic chromoendoscopy

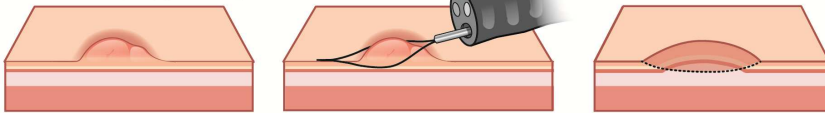
## Morphology associated with submucosal invasion

1. Paris classification III, O-IIa, or O-IIa+IIc
2. Non granular LSTs or granular LSTs with dominant nodule > 10mm
3. Kudo pit pattern type V and NICE type 3
4. Gross morphological features as spontaneous bleeding, fold convergence, surface redness, sclerous wall change, white spots, and exudates

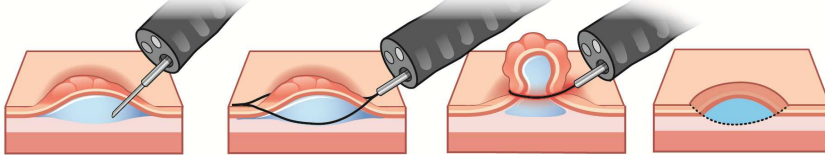
## Polypectomy with biopsy forceps



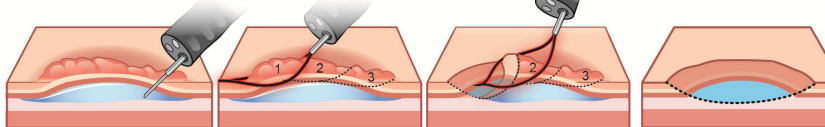
## Cold snare polypectomy



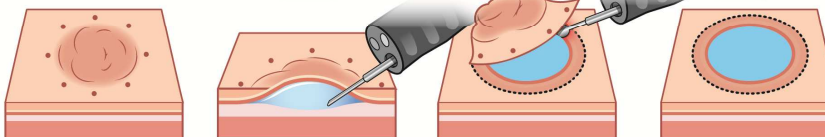
## Endoscopic mucosal resection (EMR)



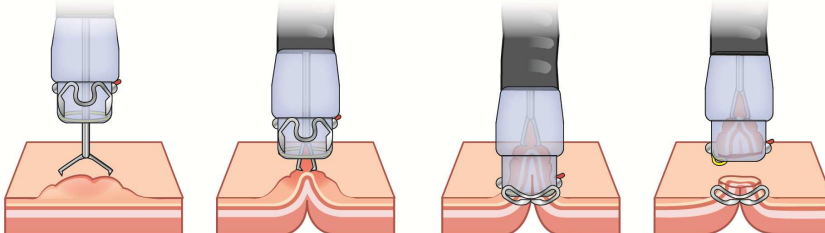
## Piecemeal endoscopic mucosal resection (pEMR)

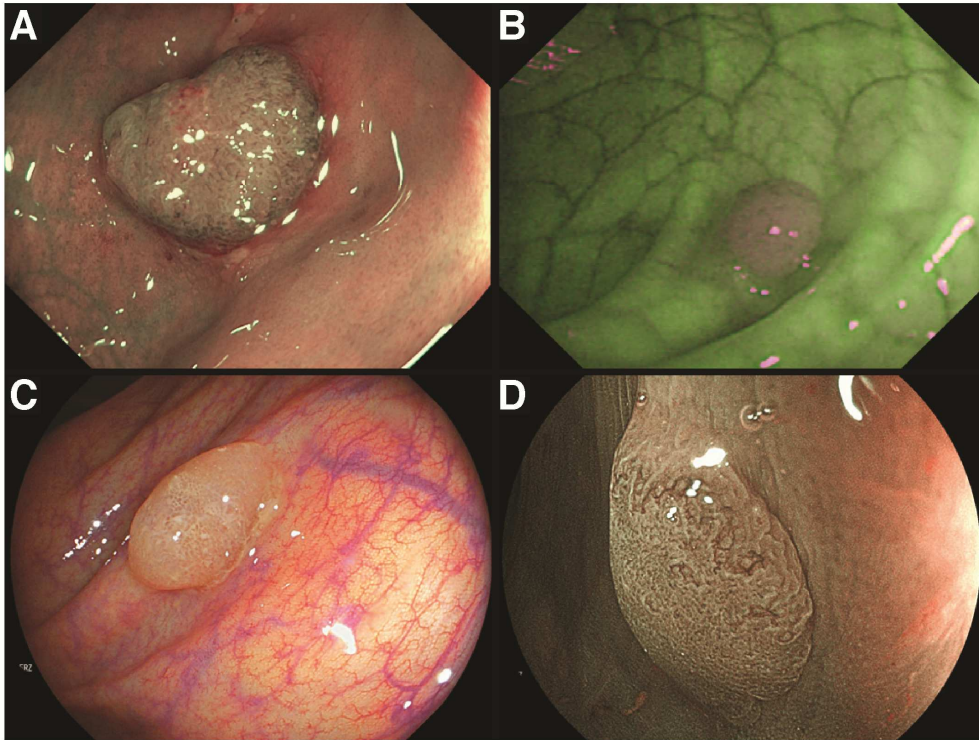


## Endoscopic submucosal dissection (ESD)



## Endoscopic full thickness resection (eFTR)







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