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Title: Narrow-band Imaging for Detection of Neoplasia at Colonoscopy: a Meta-analysis of Data From Individual Patients in Randomized Controlled Trials

Short title: NBI for Colonic Neoplasia Detection

Authors: Atkinson NSS[1,2] *, Ket S[1,3,4*], Bassett P[5], Aponte D[6], De Aguiar S[7], Gupta N[8], Horimatsu T[9], Ikematsu H[10], Inoue T[11], Kaltenbach T[12], Leung WK[13], Matsuda T[14], Paggi S[15], Radaelli F[15], Rastogi A[8], Rex DK[16], Sabbagh LC[7], Saito Y[14], Sano Y[17], Saracco GM[18], Saunders BP[19], Senore C[20], Soetiko R[12], Vemulapalli KC[16], Jairath V[21,22], East JE[1]

Affiliations:

[1] Translational Gastroenterology Unit, John Radcliffe Hospital, University of Oxford, and Oxford NIHR Biomedical Research Centre, Oxford OX3 9DU, UK; [2] Department of Gastroenterology, Waitemata District Health Board, Auckland, New Zealand; [3] Department of Gastroenterology, Alfred Hospital, Melbourne, Australia; [4] Monash University, Melbourne, Australia; [5] Stats Consultancy Ltd, Amersham, Buckinghamshire HP7 9EN, UK; [6] Gastroenterology Department, Clínica Reina Sofía, Sanitas University Foundation, Bogota, Colombia; [7] General Practice Department, Clínica Reina Sofía, Bogota, Colombia; [8] University of Kansas School of Medicine, Kansas City Veterans Affairs Medical Center, Kansas City, MO 64128-2295, USA; [9] Department of Therapeutic Oncology, Kyoto University Hospital, 54 Kawahara-cho, Shogoin Sakyo, Kyoto 606-8507, Japan; [10] Division of Science and Technology for Endoscopy, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan; [11] Second Department of Internal Medicine, Osaka Medical College, 2-7 Daigakumachi, Takatsuki 569-8686, Japan; [12] San Francisco Veterans Affairs Medical Center, University of California, San Francisco, California; [13] Department of

Medicine, Queen Mary Hospital, University of Hong Kong, 102 Pokfulam Road, Hong Kong;

[14] Endoscopy Division, National Cancer Centre Hospital, Tokyo 104-0045, Japan [15] Division of

Gastroenterology, Valduce Hospital, Como, Italy; [16] Division of

Gastroenterology/Hepatology, Department of Medicine, Indiana University School of

Medicine, Indianapolis, Indiana, USA; [17] Gastrointestinal Center and Institute of Minimally

Invasive Endoscopic Care (iMEC), Sano Hospital, Kobe, Japan; [18] Division of Gastroenterology,

Department of Medical Sciences, University of Turin, Italy; [19] Wolfson Unit for Endoscopy, St

Mark's Hospital, Imperial College London, London, UK; [20] Epidemiology and screening Unit –

CPO Piemonte; University Hospital Città della Salute e della Scienza, Turin, Italy; [21]

Department of Medicine, Western University, London, Ontario, Canada; [22] Department of

Epidemiology and Biostatistics, Western University, London, Ontario, Canada

[*] **Author names in bold designate shared co-first authorship**

Abbreviations:

ADR, adenoma detection rate ; NNT, number needed to treat ; NBI, narrow band imaging ;

OR, odds ratio ; PDR, poly detection rate ; RCT, randomized controlled trial ; RR, risk ratio ;

WLE, white light endoscopy

Correspondence:

Prof. James E East, Translational Gastroenterology Unit and Oxford NIHR Biomedical

Research Centre, Experimental Medicine Division, Nuffield Department of Clinical Medicine,

University of Oxford, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU,

UK; United Kingdom

Telephone: +44 [0]1865 228753

Fax : +44 [0]1865 228763

Email : james.east@ndm.ox.ac.uk

Disclosures:

Author contributions:

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Abstract:

Background & Aims: Adenoma detection rate (ADR) is an important quality assurance measure for colonoscopy. Some studies suggest that narrow band imaging (NBI) may be more effective at detection of adenomas than white-light endoscopy (WLE) when bowel preparation is optimal. We conducted a meta-analysis of data from individual patients in randomized controlled trials that compared the efficacy of NBI to WLE in detection of adenomas.

Methods: We searched MEDLINE, EMBASE, and Cochrane library databases, through April 2017, for randomized controlled trials that assessed detection of colon polyps by high-definition WLE vs NBI and from which data on individual patients was available. The primary outcome measure was ADR adjusted for bowel preparation quality. Multilevel regression models were used with patients nested within trials, and trial included as a random effect.

Results: We collected data from 11 trials, comprising 4491 patients and 6636 polyps detected. Adenomas were detected in 952/2251 (42.3%) participants examined by WLE vs 1011/2239 (45.2%) participants examined by NBI (unadjusted odds ratio [OR] for detection of adenoma by WLE vs NBI, 1.14; 95% CI, 1.01–1.29; *P*=.04). NBI outperformed WLE only when bowel preparation was best: adequate preparation OR, 1.07 (95% CI, 0.92–1.24; *P*=.38) vs best preparation OR, 1.30 (95% CI, 1.04–1.62; *P*=.02). Second-generation bright NBI had a better ADR than WLE (second-generation NBI OR, 1.28; 95% CI, 1.05–1.56; *P*=.02), whereas first-generation NBI did not. NBI detected more non-adenomatous polyps than WLE (OR, 1.24; 95% CI, 1.06–1.44; *P*=.008) and flat polyps than WLE (OR, 1.24; 95% CI, 1.02–1.51; *P*=.03).

Conclusions: In a meta-analysis of data from individual patients in randomized controlled trials, we found NBI to have a higher ADR than WLE, and that this effect is greater when bowel preparation is optimal.

KEY WORDS: Adenoma detection Rate; colorectal cancer; serrated polyps; tumor

Abstract Word Count : 289

Introduction

Improved adenoma detection rate (ADR) at colonoscopy is associated with a decreased risk for the development of post colonoscopy colorectal cancer.[1-3] Therefore, optimizing ADR has become a key quality indicator in the effort to make colonoscopy more effective for colorectal cancer prevention. Narrow band imaging (NBI) is a blue light technology that enhances visualization of superficial mucosal structures, especially superficial microcapillaries and has been clinically available since 2005.[4, 5] This technique has been investigated widely at colonoscopy to detect and characterise neoplastic lesions. Whilst characterisation of detected lesions has been demonstrated to be more accurate with NBI than white light, it has been more difficult to demonstrate a benefit in primary detection of dysplasia.[6, 7] As adenomas have increased vascularity and look brown with NBI against a blue-green normal background mucosa, it was hypothesized that this increased contrast might improve visualization in wide field observation. However, in five meta-analyses[8-12] using pooled data including up to 14 studies and 5074 patients, no statistically significant increase in ADR (risk or odds ratios 1.01-1.09) or polyps detected per patient was shown with NBI, and only one of four meta-analyses demonstrated an increase in flat adenomas (RR 1.96, 95% CI 1.09-3.52).[11, 13]

There has also been interest in the use of NBI to detect serrated polyps which are relatively hypovascular and look pale against the background mucosa with NBI.[14] A 3-fold increase in hyperplastic polyp detection was seen in a study of NBI in sporadic patients[15], and a subsequent single centre back-to-back study in serrated polyposis syndrome patients suggested a benefit with a polyp miss rate for NBI of 10% vs 36% for white light, P < 0.001 [16]; however this benefit was not replicated in a larger multi-centre parallel group study.[17] A

further study in sporadic patients using the new 2nd generation bright NBI also did not show a statistically significant increase in proximal serrated polyp detection, P = 0.085.[18] 2nd generation bright NBI systems available since 2012 differ from 1st generation NBI by having a stronger Xenon light source and new signal processing leading to a brighter image which might improve detection.

The issue of the importance of high-quality bowel preparation in advanced imaging with NBI has also been considered. Stool appears brick red with NBI and even a thin film of stool and mucus can significantly impair mucosal visualization. In a post hoc analysis of a parallel group randomized control trial (RCT) on NBI vs white light for detection in high risk patients, bowel preparation quality was found to be associated with polyp and adenoma detection. In patients with "good" bowel preparation there was a statistically significant benefit of NBI over white light for adenoma detection [comparison ratio 1.55 (95% CI 1.01-2.22), P = 0.04], whereas there was no difference between NBI and white light when preparation was "fair".[19]

NBI does not currently appear to increase ADR although there may be specific situations where NBI may be helpful, either in detecting flat adenomas, detecting serrated lesions, or may only work when the bowel preparation is optimal. Differences in performance of 1st vs 2nd generation bright NBI are unknown. These questions are difficult to address with meta-analysis of aggregated study level data. Accordingly, we conducted a meta-analysis of data from individual patients in RCTs which compared NBI with WLE for the detection of colonic polyps, with a primary aim to stratify for bowel preparation quality.

Methods

Search strategy and study selection

Electronic databases (MEDLINE [Ovid; 1946], EMBASE [Ovid; 1984], CENTRAL [The Cochrane library; 2017, Issue 7], and the Cochrane library) were searched from inception to April 2017 using pre-defined search terms (**Appendix A**). After the screening of citations and abstracts derived from the electronic search, complete manuscripts of potentially relevant studies were then reviewed and the selection criteria was applied.

Study eligibility criteria

Studies were eligible if they fulfilled the following criteria: (i) RCTs of high definition white light and high definition NBI 1st generation (EVIS LUCERA SPECTRUM or EXERA II; Olympus, Tokyo, Japan) or high definition NBI 2nd generation bright (EVIS LUCERA ELITE or EXERA III; Olympus, Tokyo, Japan) for the detection of colonic polyps; (ii) bowel preparation quality assessed; (iii) patient level data available for analysis. Studies focussed on inflammatory bowel disease or patients with familial or genetic syndromes e.g. Lynch syndrome or Serrated Polyposis Syndrome were excluded.

Risk of bias assessment

The Cochrane Collaboration risk of bias tool [20] was used for assessment of risk of bias by two independent investigators (SK and NA). Disagreements were resolved by discussion. Seven domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete data, selective

reporting and other potential sources of bias) were rated as having unclear, low or high risk of bias in **Appendix B**. Publication bias was assessed via a funnel plots and Begg's test.

Data synthesis and statistical analysis

Anonymised patient level data was obtained from the original investigators. The primary outcome measures used in the original data sets can be found in **Appendix C**. Due to heterogeneity of the data sets, only fields consistently collected across all studies were extracted and pooled together in a common format. These fields were age, gender, bowel preparation quality, polyp number, histology and the use of white light or NBI was collected. Specific data regarding polyp morphology, histology and location was also heterogeneous; however, total polyp number and number of adenomas were consistently recorded, thus two groups were defined; "adenomas" and "non-adenomas". Further polyp details were inconsistently available for sub-group allocation. Data was cleaned, extracted and collected per polyp in a common data format.

Additional fields such as polyp size, segmental location, indication for colonoscopy and withdrawal time were not consistently collected resulting in insufficient data for these outcomes to be included in the primary data analysis; however we were able to dichotomize colonoscopy indication into screening or non-screening, and polyp location into right side of colon (proximal to the splenic flexure) or left side of colon including the rectum.

Bowel preparation terms and classifications varied between studies. The definitions used in studies are outlined in **Appendix D**. These heterogeneous bowel preparation scores were dichotomised by identifying the cleanest bowel preparation category for each study, which

was termed 'best', and grouping all other categories as 'adequate' bowel preparation. Participants that had inadequate bowel preparation were excluded.

All analyses were performed at the patient level using multilevel regression methods. Two-level models were used, with patients nested within trials. A trial level random effect was included for each outcome to measure the treatment difference. This allowed differences in outcome between white light and NBI to vary between trials, however this did not improve the fit for any models.

Binary outcomes were analyzed using multilevel logistic regression. Outcomes relating to the number of adenomas were analysed using multilevel negative binomial regression to allow for the strongly positively skewed distributions. Where insufficient information on secondary outcomes were available, those records were included for the primary outcome and number of polyps detected, but censored from secondary analyses. A full list of the studies included in each analysis is given in **Appendix C.**

Outcome assessment

The primary outcome measures were i) ADR (proportion of patients with at least one adenoma) and ii) the ADR stratified by quality of the bowel preparation on a binary scale "best" vs "adequate" for white light vs NBI.

The secondary outcome measures were i) the number of adenomas detected, ii) the number of adenomas against quality of the bowel preparation, and iii) the polyp detection rate (PDR; proportion of patients with at least one polyp) and the number of polyps detected against quality of bowel preparation. Pre-specified polyp based subgroup analyses were performed

for non-polypoid "flat" (Paris 0-II)[21] adenomas and polyps and for non-adenomatous (presumed serrated) lesions including dichotomising for left side vs right side of the colon. Additional *a priori* exploratory analyses were performed according to biologically plausible sub-groups including age (<65 vs ≥65 years), gender, indication (screening vs non-screening), and generation of NBI system (1st vs 2nd bright generation NBI). The effect of bowel preparation quality and NBI system generation on non-adenomatous polyp detection and on flat adenoma detection was performed, as well as examining the effects of these factors in combination, specifically bowel preparation, generation of NBI system and colonoscopy indication.

Results

Search Results

The full search strategy identified 1,355 studies between 1950 and April 2017 as outlined in the PRISMA flow diagram[22] (**Figure 1, Appendix E**); however the first NBI clinical study was published in 2004. After the duplicates were removed, 1,326 articles did not meet the inclusion criteria. Thus 29 full text articles were assessed, of which 11 trials were considered eligible for inclusion. Trials were performed in Japan[23-25], Italy[26, 27], USA[18, 28, 29], Colombia[30], Hong Kong[31] and the United Kingdom.[32] Eight trials randomized patients to examination during withdrawal with either white light or NBI. The other three included trials randomized patients to tandem colonoscopy.[23, 28] In these studies, we used the first pass dataset to simulate a parallel group study, and disregarded the second pass. There was little evidence of publication bias for ADR, with most of the studies lying within the 95% confidence interval of the funnel plot (**Figure 2, Appendix F**), Begg's test P = 0.35.

Participant characteristics

A total of 4491 participants were included. The median age of the participants was 63 ± 10 years (± standard deviation, range 18-89) and 62% were male. A total of 6636 polyps were removed, of which 4920 were adenomas. 29% of participants had the 'best' bowel preparation (**Table 1**).

Primary outcome – Adenoma Detection Rate

For the primary outcome measure of ADR, 1011/2239 (45%) participants randomized to NBI had adenomas compared with 952/2251 (42%) participants randomized to WLE [unadjusted OR 1.14; 95% CI 1.01 to 1.29, P = 0.04] (**Table 2**). Comparing the ADR in the NBI group with the white light group adjusted for quality of bowel preparation, no significant difference was observed in the 'adequate' bowel prep group [OR 1.07 (95% CI 0.92 to 1.24), P = 0.38], number needed to treat (NNT) 55.6; however the odds of detecting at least one adenoma in the 'best' bowel preparation group was significantly higher with NBI compared to WLE [OR 1.30 (95% CI 1.04 to 1.62), P = 0.02], NNT 17.2.

Secondary Outcomes

When study-level was included as a random effect in the regression model, no difference was observed in model performance for the primary outcome, indicating there was no evidence the treatment effect varied by study. For the number of adenomas detected there was no significant model improvement by including a study-level random effect for treatment suggesting that there is no strong evidence that treatment effect varied by study.

There was a non-significant trend toward more adenomas detected by NBI than by white light with 10% more adenomas being detected with NBI [Ratio 1.10 (95% CI 0.99 to 1.22), P =

0.07], but no difference in the number of adenomas detected between treatment and bowel preparation quality was observed (**Table 3**). There was a significant increase in both the polyp detection rate overall with NBI [OR 1.17 (1.03 to 1.32), P = 0.01]; however, when stratified for bowel preparation quality this was only observed in the "best" prep group [OR 1.43 (1.14 to 1.79)], P = 0.002 (**Table 2**). This finding was replicated when considering polyp numbers both in terms of an increase in polyp numbers overall detected by NBI, and that this finding only retained statistical significance when bowel preparation was "best" [OR 1.18 (95% CI 1.03 to 1.63), P = 0.02], but not when adequate (**Table 3**).

Additional analyses considered the further polyp level secondary outcomes (**Table 4**); there were significant differences in favour of NBI in the odds of a patient having at least one non-adenomatous polyp [OR 1.24 (95% CI 1.06 to 1.44), P = 0.008], at least one right sided non-adenomatous polyp [OR 1.35 (95%CI 1.05 to 1.74, P = 0.02), and at least one flat polyp [OR 1.24.(95% CI 1.02 to1.51) P = 0.03]. No significant difference was observed for ADR by colonic location or for non-polypoid adenomas. **Table 5** shows how bowel preparation and NBI system generation affected the detection of non-adenomatous polyps, where a statistical trend to improved detection of non-adenomatous polyps was seen with NBI compared to white light when bowel preparation was either adequate or best, ORs 1.21 (95% CI 1.00 to 1.47) and 1.28 (95% CI 0.98 to 1.67) respectively. Similarly, NBI showed a trend towards improved detection irrespective whether 1st or 2nd generation bright NBI systems were used ORs 1.22 (95% CI 1.00 to 1.50) and 1.24 (95% CI 0.97 to 1.58) respectively. Results for the secondary outcomes measured on a continuous scale are summarized in **Table 8** (**Appendix G**), with confirmation of a significant difference for total numbers non-adenomatous polyps in favour of NBI [OR 1.26 (1.09 to 1.46), P = 0.003]. In a post hoc analysis for the effect of bowel preparation on the detection of flat (non-polypoid)

adenomas, NBI detected significantly more flat adenomas when bowel preparation was best [OR 1.45 (1.01 to 2.07)], P = 0.05, but not when adequate (**Table 9**, **Appendix G**)

NBI performed significantly better than white light for non-screening patients than for screening patients both in terms of ADR [OR 1.27 (95% CI 1.09 to 1.49), P = 0.003, and in total numbers of adenomas detected (**Table 6 and Table 9, Appendix G**). Similar results were seen for number of polyps detected (**Table 11, Appendix G**). The odds of detecting at least one adenoma with 2nd generation bright NBI vs white light was significantly higher than with WLE (OR 1.28 (95% CI 1.05 to 1.56), P = 0.02; however, this effect was not observed for 1st generation NBI [OR 1.06 (95% CI 0.91 to 1.24), P = 0.48] (**Table 6**). This effect of generation of NBI system was not statistically significant when number of adenomas were considered (**Table 10, Appendix G**) but was statistically significant when number of polyps were considered for 2nd generation bright NBI vs WLE [OR 1.20 (95% CI 1.05 to 1.37), P = 0.007] (**Table 11, Appendix G**).

Table 7 shows the results of the combined effects on polyp detection after stratification by bowel preparation, NBI system generation and colonoscopy indication. No statistically significant interaction was seen for adenoma detection; however there was some evidence of interaction for polyps detection rate for NBI generation and bowel preparation when colonoscopy indication was removed from the model (interaction p-value P = 0.08 and P = 0.04 respectively). Accounting for colonoscopy indication (screening vs non-screening), no significant difference when preparation was adequate with 1st generation NBI; however, both 1st and 2nd generation bright NBI were associated with significantly higher polyp detection rates in those with a "best" prep, and also if the prep was adequate using the new 2nd generation bright NBI. The largest effect was for patients with a "best" prep using 2nd

generation bright NBI, where the odds of detection were more than 60% higher with NBI than for WLE [OR 1.64 (95% CI 0.25 to 2.16)], P < 0.001.

Discussion

This is the first meta-analysis that utilized individual patient level data from RCTs comparing 1st and 2nd generation high definition NBI vs high definition WLE, that also defined bowel preparation quality, with ADR as an outcome. Our main finding indicated a statistically significant 14% increase in the odds of detecting at least one adenoma for NBI compared to WLE when the data was combined from 4491 patients across six countries, but not in the total number of adenomas detected. Furthermore, this improvement in ADR with NBI only maintained statistical significance when bowel preparation was stratified to "best" quality. This effect of bowel preparation remained consistent when the analysis was conducted for polyp detection rate and for when the numbers of polyps were considered (**Tables 2 and 3**), and when we controlled for generation of NBI system and colonoscopy indication (**Table 7**)

Previous studies have suggested that bowel preparation scores correlate with polyp detection, both in the use of WLE alone[33] and NBI over white light.[19] In a previous study we found that when bowel preparation was good, NBI performed significantly better than WLE for total polyp number and adenoma detection[19], but there was no difference between the NBI and WLE group when the bowel preparation was only fair. In contrast, the individual findings of Sabbagh[30] and Kaltenbach[28] did not demonstrate this effect. In the current meta-analysis of data from individual patients in RCTs, when the preparation was "best", NBI was associated with a 5.8% increase in the ADR, with a NNT of 17.2. This is consistent with the idea that for advanced endoscopic imaging optimal bowel preparation is required, and that even slightly sub-optimal bowel preparation may negate the benefits. When the preparation

was only adequate, the ADR only increased by an absolute 1.8%, and NNT rises to 55.6; however, when we analysed for non-adenomatous polyps stratified for bowel preparation, NBI improved detection for both adequate and best preparation (**Table 5**). Studies in colonoscopy screening programmes or in community based cohorts have indicated that for serrated polyps optimal bowel preparation did not lead to improved serrated lesion detection[34, 35]. A hypothesis to explain this may be that adherent stool on serrated lesions may help direct the endoscopist investigate the mucosal surface more carefully to detect these subtle lesions, which might be washed off by "best" bowel preparation.

Unlike prior meta-analyses, we were able to include three 2nd generation bright NBI studies in our study with patient level data. When we stratified for this modality, we found that use of NBI led to significantly more patients with least one adenoma detected with 2nd generation bright NBI, but not with 1st generation NBI, with the odds of detecting at least one patient with an adenoma being 28% higher with 2nd generation bright NBI vs 6% with 1st generation NBI (**Table 6**). A similar result was seen for number of polyps detected overall. This finding is consistent with another next generation bright blue light advanced imaging system, Blue-laser imaging (BLI; LASEREO; Fujifilm Co, Tokyo, Japan), which superseded the darker Flexible spectral Imaging Color Enhancement (FICE; Fujifilm Co, Tokyo, Japan) system. FICE did not improved ADR in meta-analysis[12], whereas BLI appears to increase mean adenomas detected and reduces adenoma miss rates in early studies[36, 37]

The role of NBI in the detection of non-adenomatous polyps has been unclear. We found that NBI is beneficial for the detection of non-adenomatous polyps, both numbers of patients with at least one non-adenomatous polyp detected and in numbers of non-

adenomatous polyps (**Table 4**). This increase in non-adenomatous polyp detection was also seen in the study by Paggi and colleagues[27], and was of borderline statistical significance in the study by Rex and colleagues[18]. From this patient level data, it is unclear what proportion of the non-adenomatous polyps were sessile serrated polyps. However, when the analysis was limited to non-adenomatous polyps in the proximal colon which are more likely to be sessile serrated polyps, the results remained statistically significant for patients with at least one non-adenomatous polyp, although this should be interpreted with caution due to the smaller sample size. We also investigated the role of NBI system generation in the detection of non-adenomatous polyps, where there was a statistical trend to improved non-adenomatous polyp detection with either 1st or 2nd generation bright NBI, in contrast to the data for adenoma detection where only 2nd generation bright NBI significantly improved detection (**Table 5 and 6**). Increasing evidence highlights the clinical importance of sessile serrated polyps and their role in interval cancers.[38, 39] This is of concern due to the difficulty in endoscopic detection, both due to their flat nature but also that sessile serrated polyps with dysplasia or malignancy are small, with a median polyp size of 9mm, and that in 83% the neoplastic component is flat.[40]

We also considered whether non-polypoid "flat" (Paris 0-II) adenomas might be better detected with NBI, with one study level meta-analysis suggesting a benefit, with a relative Risk, 1.96; 95% CI, 1.09–3.52[11], though three other study level meta-analyses were negative[8-10]. Our study confirms that the odds of patients having at least one non-polypoid "flat" polyp was increased by 24% using NBI, but we did not demonstrate a significant effect for having at least one non-polypoid adenoma. This may be driven by the increase in non-adenomatous polyps with NBI where serrated polyps are much more likely to be non-polypoid. However,

we did find an increase in non-polypoid adenoma detection when bowel preparation was "best" (**Table 9, Appendix G**) which is again consistent with the concept that bowel preparation needs to be optimised for adenoma detection with NBI.

There are number of possibilities why this individual patient level data meta-analysis found significant differences between NBI and WLE, in contrast to previous meta-analyses. First, the current dataset represents the largest to date for sporadic lesions both in terms of patient numbers, polyp numbers and number of studies, leading to greater statistical power to detect smaller differences. Second, our unique ability to look at patient level factors including bowel preparation, polyp pathology, morphology and position in the colon, sex, colonoscopy indication, age and generation of NBI has allowed further insights to be obtained not possible from study level data. Third, we included data from 2nd generation bright NBI studies which seemed to perform better than 1st generation NBI. Fourth, we were able to investigate the effects of bowel preparation and NBI system generation in combination on polyp detection.

Several limitations from this study should be acknowledged. First, the data sets were somewhat heterogeneous and are not precisely aligned in descriptors used and did not all report all outcomes in a consistent way. Nevertheless, the level of detail available substantially exceeds other meta-analyses and the heterogeneity in outcome reporting is a well-recognized problem in clinical trials. Secondly, since we focused on the effect of bowel preparation on NBI performance as our primary outcome, we may have excluded studies reporting on our secondary outcomes, although, our patient level sample sets included at least three studies.

Third, we had limited histological information on non-adenomatous polyps or their size, which may be relevant as small non-adenomatous polyps may not be clinically important. Many studies were started prior to the appreciation of the importance of sessile serrated polyps, and may not have had the histopathological expertise to report these. Therefore, not all non-adenomatous polyps will be of the serrated class, and of the serrated class polyps not all will be sessile serrated polyps. However, when the results are sub-analysed to only examine the non-adenomatous polyps in the right colon to avoid contamination by multiple rectal hyperplastic polyps, a significant difference persisted. Fourth, we did not include patients with ulcerative colitis or those at high genetic risk e.g. Lynch syndrome or serrated polyposis syndrome. Fifth, the size of the clinical benefit seen is limited, for example a 2.9% absolute benefit in ADR in all studies of NBI vs WLE, though larger absolute benefits were seen with "best" bowel preparation and 2nd generation bright NBI, 5.8% and 6.0% respectively. The greatest benefit was seen when both prep was best and 2nd generation bright NBI was used with an associated 60% relative increase in ADR. This should be seen in the context of expert performance with high definition WLE with a baseline ADR of more than 40%. Sixth, not all analyses that showed significance in a binary analysis e.g. ADR, also showed significance in when analysed as a continuous variable e.g. adenoma number. This may reflect the "one and done" phenomenon, where once one adenoma is detected the endoscopist is less motivated to keep searching for further lesions[41] . Finally, the number of sub-group analyses is high risking a false positive result by chance, and therefore results of secondary analyses should be considered exploratory or hypothesis generating.

In conclusion, in this large meta-analysis of data from 4491 individual patients in randomized controlled trials, we found NBI significantly improved ADR compared to high definition WLE

and was consistent with our hypothesis that this effect is greater when bowel preparation is

optimal. Secondary subgroup analysis suggests that 2nd generation bright NBI improved ADR,

and that NBI was more effective for detecting non-adenomatous polyps.

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Tables

Table 1: Study demographics

Study	# of patients	Age [$]	Male Gender	Screening Indication	Total # of polyps	Total # of adenomas	Best prep
East (UK)	214	64 ± 9	60%	28%	606	422	33%
Horimatsu (Japan)	431	64 ± 12	67%	0%	760	643	28%
Ikematsu (Japan)	782	63 ± 10	70%	6%	772	583	32%
Kaltenbach (USA)	266	64 ± 10	97%	52%	399	-	43%
Leung (Hong Kong)	360	62 ± 11	48%	10%	395	300	9%
Paggi (Italy)	210	60 ± 5	55%	-	485	398	50%
Rastogi (USA)	439	61 ± 9	64%	64%	757	529	8%
Rex (USA)	799	61 ± 8	43%	50%	1407	1023	48%
Sabbagh (Colombia)	478	58 ± 13	37%	72% [*]	196	-	4%
Saracco (Italy)	269	71 ± 3	57%	100%	357	234	22%
Inoue (Japan)	243	62 ± 12	62%	0%	202	158	60%
Total	**4491**	**63 ± 10**	**62%**	**33%**	**6636**	**4290** [+]	**29%**

($) Figures are mean ± standard deviation
(*) Based on data from 86/472 patients only
(+) Based on data from 9/11 studies only

Table 2: Analysis results for adenoma detection rate and polyp detection rate stratified by bowel preparation quality

Bowel preparation	N. studies	WLE % (n/N)	NBI % (n/N)	Odds Ratio [*] (95% CI)	P-value
Adenomas					
All	11	42.3% (952/2251)	45.2% (1011/2239)	1.14 (1.01, 1.29)	**0.04**
Adequate	11	41.4% (638/1543)	43.2% (702/1625)	1.07 (0.92, 1.24)	0.38
Best	11	44.4% (314/707)	50.2% (307/612)	1.30 (1.04, 1.62)	**0.02**
Polyps					
All	11	53.4% (1203/2251)	56.9% (1274/2240)	1.17 (1.03, 1.32)	**0.01**
Adequate	11	52.6% (812/1543)	54.4% (883/1622)	1.07 (0.92, 1.24)	0.37
Best	11	55.2% (391/708)	63.1% (388/615)	1.43 (1.14, 1.79)	**0.002**

(*) Calculated as odds of adenoma detection in NBI group relative to odds in WLE group

Table 3: Analysis results for number of adenomas and polyps stratified by bowel preparation quality

Bowel Preparation	N. studies	WLE N	Mean (SD)	NBI N	Mean (SD)	Ratio [*] (95% CI)	P-value
Adenomas							
All	9	1876	1.09 (1.82)	1870	1.20 (1.87)	1.10 (0.99, 1.22)	0.07
Adequate	9	1233	1.10 (1.85)	1321	1.20 (1.90)	1.08 (0.96, 1.22)	0.21
Best	9	642	1.08 (1.76)	547	1.19 (1.82)	1.13 (0.94, 1.35)	0.18
Polyps							
All	11	2252	1.33 (1.96)	2239	1.49 (2.12)	1.12 (1.03, 1.21)	**0.006**
Adequate	11	1543	1.29 (1.95)	1622	1.43 (2.10)	1.08 (0.98, 1.19)	0.10
Best	11	708	1.43 (2.00)	615	1.64 (2.17)	1.18 (1.03, 1.63)	**0.02**

(*) Calculated as number of adenomas in NBI group relative to number in WLE group

Table 4: Secondary outcomes for detection rates by polyp pathology, morphology or location sub-groups

Outcome	N. studies	WLE % (n/N)	NBI % (n/N)	Odds Ratio [*] (95% CI)	P-value
Non-adenomas	9	20.7% (388/1876)	24.2% (453/1870)	1.24 (1.06, 1.44)	**0.008**
Non-adenomas [+]	6	9.7% (123/1263)	12.7% (160/1260)	1.35 (1.05, 1.74)	**0.02**
Non-polypoid ad.	5	17.7% (199/1124)	18.9% (213/1130)	1.10 (0.87, 1.37)	0.43
Adenoma [+]	6	32.7% (413/1262)	35.2% (444/1261)	1.12 (0.95, 1.32)	0.19
Adenoma [++]	6	15.9% (200/1262)	17.9% (226/1261)	1.22 (0.97, 1.53)	0.09
Flat polyps	6	21.2% (267/1260)	24.5% (309/1260)	1.24 (1.02, 1.51)	**0.03**

(*) Calculated as odds of detection in NBI group relative to odds in WLE group
(+) Right side colon only
(++) Left side colon only

Table 5: Analysis results for non-adenomatous polyp detection rate stratified by bowel preparation quality and NBI system generation

Subgroup	N. studies	WLE % (n/N)	NBI % (n/N)	Odds Ratio [*] (95% CI)	P-value
Adequate prep	9	19.6% (242/1223)	22.6% (298/1318)	1.21 (1.00, 1.47)	0.05
Best prep	9	22.7% (146/643)	27.7% (152/549)	1.28 (0.98, 1.67)	0.08
1st Generation NBI	6	21.9% (236/1078)	25.3% (273/1078)	1.22 (1.00, 1.50)	0.05
2nd Generation bright NBI	3	19.2% (153/799)	22.6% (179/791)	1.24 (0.97, 1.58)	0.09

(*) Calculated as odds of non-adenoma detection in NBI group relative to odds in WLE group

Table 6: Subgroup analysis of adenoma detection rate according to patient characteristics and NBI system generation

Subgroup	N. studies	WLE % (n/N)	NBI % (n/N)	Odds Ratio [*] (95% CI)	P-value
Age					
<65	11	37.5% (463/1234)	40.1% (516/1288)	1.14 (0.96, 1.34)	0.14
≥ 65	11	48.1% (489/1017)	52.1% (495/951)	1.17 (0.97, 1.40)	0.10
Gender					
Female	11	33.1% (311/940)	35.7% (334/936)	1.13 (0.93, 1.38)	0.21
Male	11	48.9% (641/1311)	52.0% (677/1303)	1.15 (0.98, 1.35)	0.09
Indication					
Screening	8	41.1% (259/631)	39.9% (264/661)	0.99 (0.79, 1.25)	0.94
Non-scr.	9	45.8% (601/1311)	51.6% (663/1284)	1.27 (1.09, 1.49)	**0.003**
NBI system					
1st Generation NBI	8	39.9% (579/1452)	41.0% (594/1448)	1.06 (0.91, 1.24)	0.48
2nd Generation bright NBI	3	46.7% (373/799)	52.7% (417/791)	1.28 (1.05, 1.56)	**0.02**

Table 7: Analysis for combined colonoscopy indication, bowel preparation and NBI results for polyp detection rate

Colonoscopy Indication adjustment	Subgroup	Odds Ratio [*] (95% CI)	Modality P-value
Yes	Adequate prep + 1st generation NBI	1.07 (0.88, 1.29)	0.50
	Adequate prep + 2nd generation NBI	1.28 (1.02, 1.60)	**0.03**
	Best prep, + 1st generation NBI	1.36 (1.04, 1.76)	**0.02**
	Best prep + 2nd generation NBI	1.62 (1.22, 2.14)	**0.001**
No	Adequate prep + 1st generation NBI	0.99 (0.83, 1.17)	0.88
	Adequate prep + 2nd generation NBI	1.24 (0.99, 1.55)	0.06
	Best prep, + 1st generation NBI	1.31 (1.02, 1.68)	**0.03**
	Best prep + 2nd generation	1.64 (0.25, 2.16)	**<0.001**

	NBI

(*) Calculated as odds of detection in NBI group relative to odds in WLE group

Supplementary material

Appendix A: Search strategy

MEDLINE search strategy 1950 to 1.4.2017

1	Adenoma/
2	exp Adenomatous Polyps/
3	exp Intestinal Polyps/
4	(adenoma* or polyp?).ti,ab.
5	((colon* or colorectal) adj3 polyp*).ti,ab.
6	exp Colorectal Neoplasms/
7	1 or 2 or 3 or 4 or 5 or 6
8	endoscopy/ or exp endoscopy, digestive system/
9	(endoscop* or colonoscop*).ti,ab.
10	8 or 9
11	(narrow band* or narrowed band or narrow spectrum or narrowed spectrum).ti,ab.
12	10 and 11
13	((narrow band* or narrowed band or narrow spectrum or narrowed spectrum) adj3 imaging).ti,ab.
14	(nbi adj3 (endoscop* or colonoscop*)).ti,ab.
15	nbi.ti.
16	electronic chromoendoscop*.ti,ab.
17	12 or 13 or 14 or 15 or 16
18	7 and 17
19	randomized controlled trial.pt.
20	controlled clinical trial.pt.
21	randomized.ab.
22	placebo.ab.
23	drug therapy.fs.
24	randomly.ab.
25	trial.ab.
26	groups.ab.
27	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28	exp animals/ not humans.sh.
29	27 not 28
30	18 and 29
31	18 not 29

EMBASE search strategy 1950 to 1.4.2017

1	Adenoma/
2	*polyp/ or adenomatous polyp/ or exp intestine polyp/
3	(adenoma* or polyp?).ti,ab.
4	((colon* or colorectal) adj3 polyp*).ti,ab.
5	exp *colon tumor/ or exp *rectum tumor/
6	1 or 2 or 3 or 4 or 5
7	exp digestive tract endoscopy/ or endoscopy/
8	(endoscop* or colonoscop*).ti,ab.
9	7 or 8
10	(narrow band* or narrowed band or narrow spectrum or narrowed spectrum).ti,ab.
11	9 and 10
12	narrow band imaging/
13	((narrow band* or narrowed band or narrow spectrum or narrowed spectrum) adj3 imaging).ti,ab.
14	(nbi adj3 (endoscop* or colonoscop*)).ti,ab.
15	nbi.ti.
16	electronic chromoendoscop*.ti,ab.
17	11 or 12 or 13 or 14 or 15 or 16
18	6 and 17
19	randomized controlled trial/
20	single blind procedure/ or double blind procedure/
21	crossover procedure/
22	random*.tw.
23	((singl* or doubl*) adj (blind* or mask*)).tw.
24	(crossover or cross over or factorial* or latin square).tw.
25	(assign* or allocat* or volunteer*).tw.
26	19 or 20 or 21 or 22 or 23 or 24 or 25
27	18 and 26
28	18 not 26

Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library), 2017

#1	MeSH descriptor: [Adenoma] this term only
#2	MeSH descriptor: [Adenomatous Polyps] explode all trees
#3	MeSH descriptor: [Intestinal Polyps] explode all trees
#4	(adenoma* or polyp?):ti,ab,kw (Word variations have been searched)
#5	MeSH descriptor: [Colorectal Neoplasms] explode all trees
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Endoscopy] this term only
#8	MeSH descriptor: [Endoscopy, Digestive System] explode all trees
#9	endoscop* or colonoscop*:ti,ab,kw (Word variations have been searched)
#10	#7 or #8 or #9
#11	narrow band* or narrowed band or narrow spectrum or narrowed spectrum:ti,ab,kw (Word variations ha searched)
#12	#11 and #10
#13	((narrow band* or narrowed band or narrow spectrum or narrowed spectrum) near imaging):ti,ab,kw (W variations have been searched)

#14   (nbi near (endoscop* or colonoscop*)):ti,ab,kw (Word variations have been searched)

#15   nbi:ti (Word variations have been searched)

#16   electronic chromoendoscop*:ti,ab,kw (Word variations have been searched)

#17   #12 or #13 or #14 or #15

#18   #6 and #17

Appendix B: Risk of bias assessment

Cochrane Criteria	East	Horimatsu	Ikematsu	Inoue	Kaltenbach	Leung	Paggi	Rastogi	Rex	Sabbagh	Saracco
Random sequence generation	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Allocation concealment	Low	Unclear	Low	Low	Low	Low	Low	Low		Low	Low
Blinding of participants and personnel	High	High	High	High	Unclear	High	High	High	High	High	High
Blinding of outcome assessment	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Incomplete outcome data	Low	Low	Low	Unclear	Low	Low	Low	Unclear	Low	Low	Low
Selective reporting	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Other bias	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low

Appendix C: **Summary of studies included in each analysis**

Outcome	Amit	East	Horimatsu	Ikematsu	Kaltenbach	Leung	Paggi	Rex	Sabbagh	Saracco	Takuya
Adenoma – Yes/no	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adenoma – Number	✓	✓	✓	✓		✓	✓	✓		✓	✓
Polyps – Yes/no	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Polyps – Number	✓	✓		✓	✓		✓		✓	✓	✓
Non-adenomas – Yes/no	✓	✓	✓	✓		✓	✓	✓		✓	✓
Non-adenomas – Number	✓	✓	✓	✓		✓	✓			✓	✓
Non-aden. right c. – Yes/no	✓		✓	✓		✓				✓	✓
Non-aden. right c. – Number	✓		✓	✓		✓				✓	✓
Non-polypoid aden. – Y/N	✓		✓	✓		✓					✓
Non-polypoid aden. – Number	✓		✓	✓		✓					✓
Adenomas right c. – Y/N	✓		✓	✓		✓				✓	✓
Adenomas right c. – Number	✓		✓	✓		✓				✓	✓
Adenomas left c. – Yes/no	✓		✓	✓		✓				✓	✓
Adenomas left c. – Number	✓		✓	✓		✓				✓	✓

Appendix D: Definitions of bowel preparation scores in original articles

Study	Excellent/ Optimal	Good	Adequate	Sub-Optimal	Fair	Poor	Inadequate
East		No more than liquid residue that could be aspirated to achieve near 100% visualization	> 90% visualization			< 90% visualization - Excluded	
Horimatsu	100% mucosal visualization following suction of fluid residue	90% mucosal visualization			<90% mucosal visualization	Large amounts of solid fecal matter - Excluded	
Ikematsu	Approximately 100% mucosal visualization following suction of fluid residue	Approximately 90% mucosal visualization			Less than 90% mucosal visualization	Large amounts of solid fecal matter were found - Excluded	
Inoue		Near 100% mucosal visualization after aspiration of liquid residue			Greater than 90% mucosal visualization	Less than 90% mucosal visualization - excluded	
Kaltenbach	Small volume of clear liquid or greater than 95% of surface seen	Large volume of clear liquid covering 5% to 25% of the surface but greater than 90% of surface seen			Some semi-solid stool that could be suctioned or washed away but greater than 90% of surface seen.	Semi-solid stool that could not be suctioned or washed away and less than 90% of surface seen	Repreparation needed - Excluded
Leung	~100% of colonic mucosal visualization	~95% mucosal visualization			> 90% mucosal visualization	< 90% mucosal visualization	
Paggi	Minimal amount of liquid stools	Mainly liquid stools, frequent aspiration needed, no limitation of the			Liquid and semisolid stools, frequent aspiration and washings needed;		More than 10% of mucosa not visualized, presence of solid

|		examination			small lesions might be missed		or semisolid stools; aspiration not possible, repetition of the examination required - Excluded
Sabbagh	Excellent	Good		Fair		Poor - Excluded	Inadequate - Excluded
Saracco	Minimal amount of liquid stools		Mainly liquid stools, no limitation of the examination	Liquid and semisolid stools - Excluded			Impossible to perform a reliable examination, repetition of procedure required - Excluded
Rastogi	> 90% of mucosa seen, mostly liquid colonic contents, minimal suctioning needed for adequate visualization	> 90% of mucosa seen, mostly liquid colonic contents, significant suctioning needed for adequate visualization		> 90% of mucosa seen, mixture of liquid and semisolid colonic contents, could be suctioned and/or washed			< 90% of mucosa seen, mixture of semisolid and solid colonic contents, which could not be suctioned or washed - Excluded
Rex	Excellent	Good		Fair			Too difficult to correct with intraprocedural washing procedures - Not randomised

Appendix E: Figure 1. PRISMA flow chart of study selection
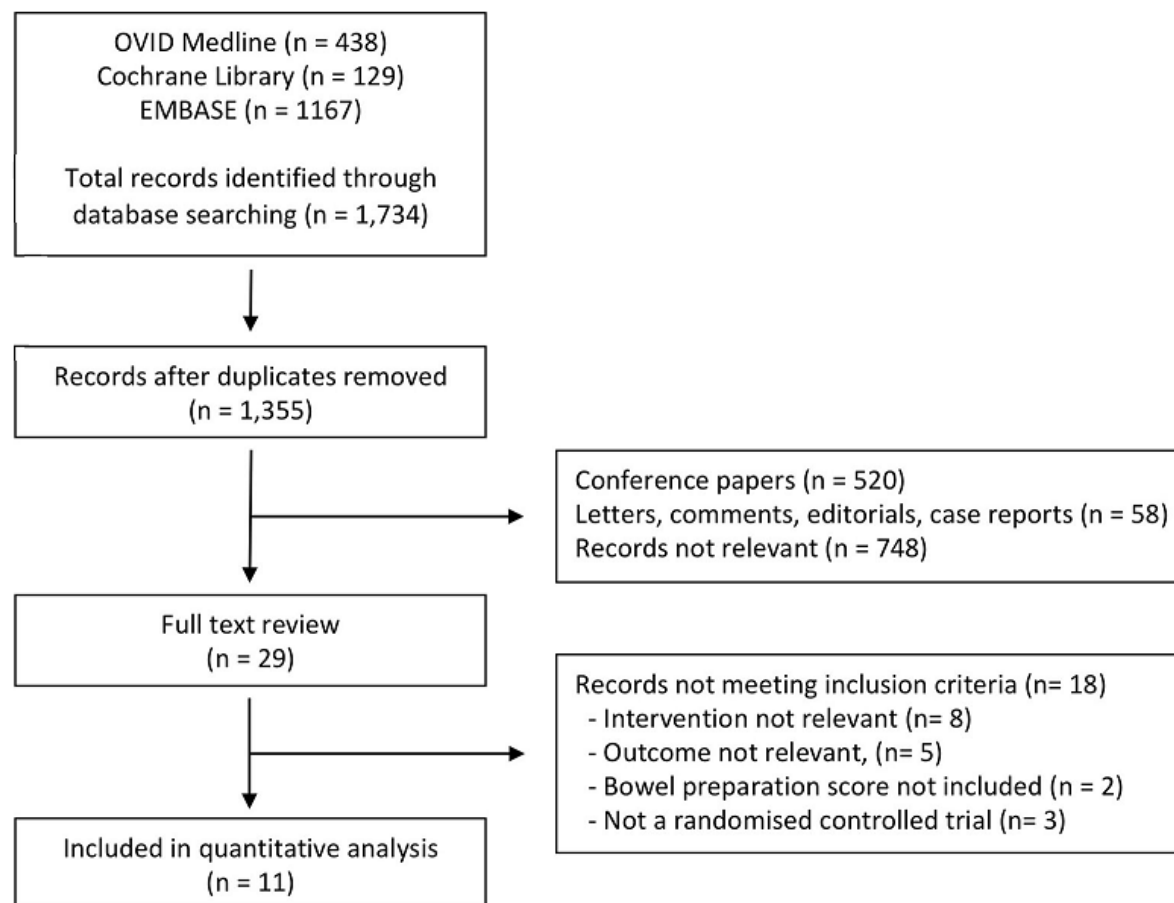
Appendix F: Figure 2. Funnel plot to assess publication bias for adenoma detection rate
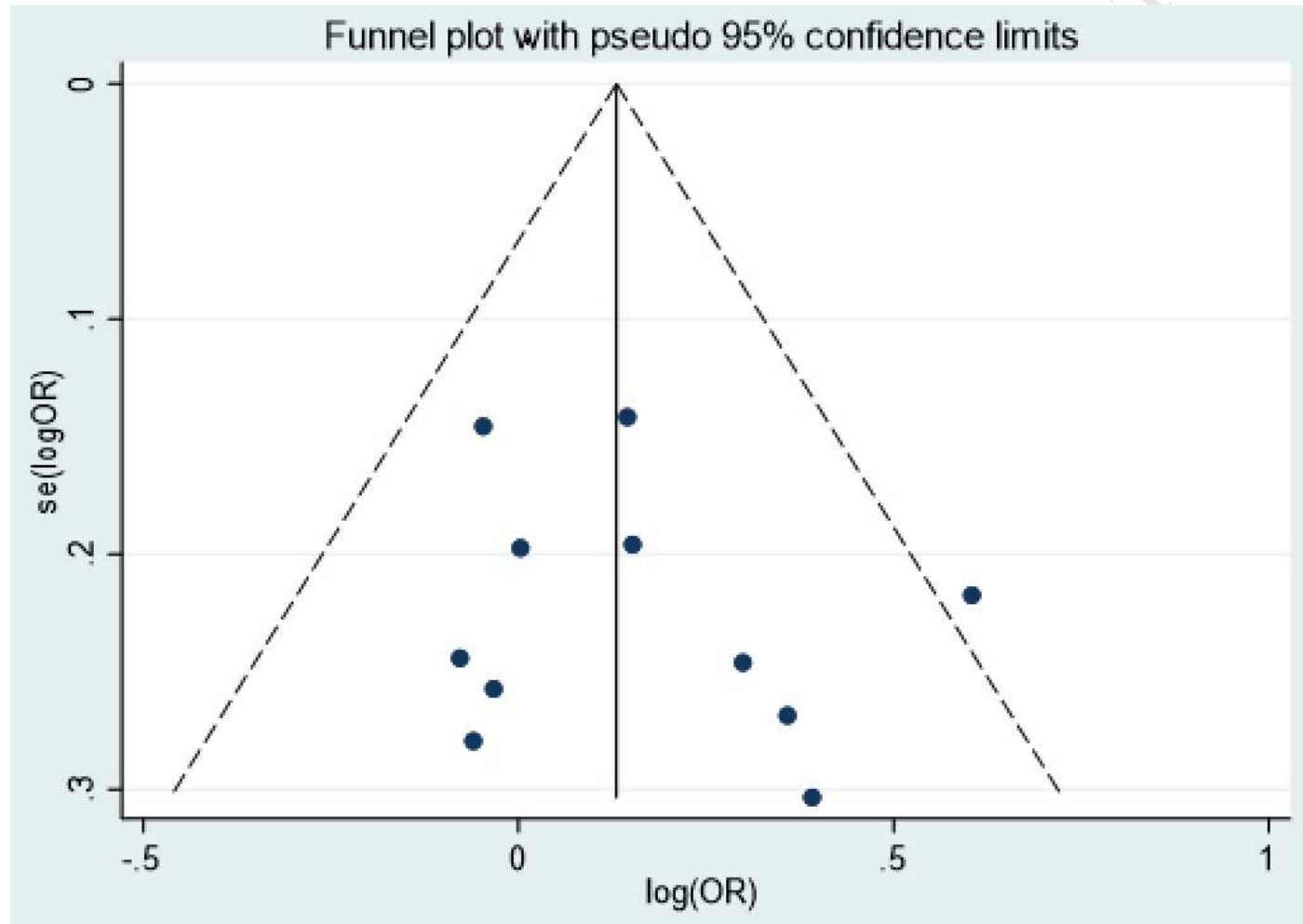
Appendix G: Additional data tables

Table 8: Secondary outcomes for detection numbers by polyp pathology, morphology or location sub-groups

Outcome	N. studies	WLE Mean (SD)	NBI Mean (SD)	Ratio [*] (95% CI)	P-value
Non-adenomas	9	0.33 (0.84)	0.41 (0.95)	1.26 (1.09, 1.46)	**0.003**
Non-adenomas [+]	6	0.16 (0.71)	0.18 (0.56)	1.15 (0.88, 1.50)	0.30
Non-polypoid ad	5	0.32 (0.91)	0.33 (0.89)	1.00 (0.80, 1.24)	0.97
Adenoma [+]	6	0.67 (1.45)	0.76 (1.48)	1.13 (0.97, 1.31)	0.11
Adenoma [++]	6	0.24 (0.65)	0.27 (0.70)	1.17 (0.97, 1.43)	0.11
Flat polyps	6	0.40 (1.03)	0.46 (1.06)	1.09 (0.91, 1.31)	0.35

(*) Calculated as number in NBI group relative to number in WLE group
(+) Right side colon only

Table 9. Detection of non-polypoid "flat" adenomas stratified by bowel preparation quality and NBI generation

Subgroup	N. studies	WLE % (n/N)	NBI % (n/N)	Odds Ratio [*] (95% CI)	P-value
Adequate prep	6	19.7% (174/883)	22.5% (213/945)	1.17 (0.92, 1.48)	0.21
Best prep	6	24.7% (93/377)	30.5% (96/315)	1.45 (1.01, 2.07)	0.05
1st Generation NBI	4	19.8% (171/862)	23.4% (203/867)	1.25 (0.99, 1.59)	0.06
2nd Generation "bright" NBI	2	24.1% (96/398)	22.6% (106/393)	1.20 (0.85, 1.70)	0.29

(*) Calculated as number of adenomas in NBI group relative to number in WLE group

Table 10: Subgroup analysis of adenoma numbers according to patient characteristics and NBI system generation

Subgroup	N. studies	WLE N	Mean (SD)	NBI N	Mean (SD)	Ratio (*) (95% CI)	P-value
Age <65	9	1003	0.96 (1.70)	1028	1.04 (1.73)	1.07 (0.92, 1.24)	0.37
Age 65+	9	873	1.25 (1.94)	842	1.39 (2.02)	1.13 (0.99, 1.30)	0.07
Female	9	791	0.74 (1.32)	777	0.92 (1.69)	1.20 (1.01, 1.43)	**0.04**
Male	9	1085	1.35 (2.07)	1093	1.40 (1.97)	1.05 (0.93, 1.19)	0.40
Screening	6	532	0.99 (1.94)	561	1.02 (1.78)	1.05 (0.85, 1.30)	0.64
Non-scr.	7	1237	1.07 (1.73)	1205	1.21 (1.85)	1.14 (1.01, 1.28)	**0.04**
1st Generation NBI	6	1077	1.04 (1.78)	1079	1.12 (1.84)	1.08 (0.94, 1.23)	0.28
2nd Generation "bright" NBI	3	799	1.17 (1.88)	791	1.31 (1.92)	1.13 (0.97, 1.31)	0.12

(*) Calculated as number of adenomas in NBI group relative to number in WLE group

Table 11: Subgroup analysis of polyp numbers according to patient characteristics and NBI system generation

Subgroup	N. studies	N	WLE Mean (SD)	N	NBI Mean (SD)	Ratio [*] (95% CI)	P-value
Age <65	11	1234	1.16 (1.82)	1287	1.29 (1.94)	1.11 (0.99, 1.24)	0.08
Age 65+	11	1018	1.54 (2.10)	952	1.77 (2.31)	1.14 (1.02, 1.28)	**0.02**
Female	11	940	0.92 (1.50)	937	1.14 (1.89)	1.20 (1.04, 1.38)	**0.01**
Male	11	1312	1.63 (2.19)	1302	1.74 (2.24)	1.09 (0.99, 1.19)	0.09
Screening	8	631	1.33 (2.10)	661	1.39 (1.95)	1.06 (0.91, 1.24)	0.47
Non-scr.	9	1311	1.39 (1.94)	1285	1.65 (2.24)	1.19 (1.08, 1.31)	**0.001**
1st Generation NBI	8	1453	1.25 (1.88)	1448	1.35 (2.01)	1.07 (0.97, 1.18)	0.20
2nd Generation "bright" NBI	3	799	1.47 (2.09)	791	1.75 (2.29)	1.20 (1.05, 1.37)	**0.007**

[*] Calculated as number of adenomas in NBI group relative to number in WLE group

Individual patient level data meta-analysis for high definition White Light Endoscopy (WLE) vs Narrow Band Imaging (NBI) stratified by bowel preparation

11 international centers

4491 individual patient datasets

Gastroenterology