Aspects of quality in colonoscopy

Post-colonoscopy colorectal cancer, individualized training programmes, assessing colonoscopy adverse events and standardized/overall colonoscopy performance indicators

Pedersen, Lasse Jan

Publication date:
2020

Document Version
Publisher's PDF, also known as Version of record

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BY
LASSE JAN PEDERSEN

DISSERTATION SUBMITTED 2020

AALBORG UNIVERSITY
DENMARK

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ISSN (online): 2246-1302
ISBN (online): 978-87-7210-809-4

Published by:
Aalborg University Press
Kroghstræde 3
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Rosendahls, 2020

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ACKNOWLEDGEMENTS

I would like to thank my main supervisor, Inge Bernstein, for endless support and believing in my abilities. She has managed to navigate through bureaucracy and financing and she is without doubt the main reason that I have managed to complete this PhD thesis. I would also like to thank my assistant PhD supervisors Charlotte Green and Karen Lindorff-Larsen. They initially signed up for a "colonoscopy training" PhD, but as recuitment slowed they found themselves in new territory among epidemiology studies and performance indicators. Their dedication has remained impressively unaffected. I would also like to thank Christian Torp-Pedersen for endless hours of teaching Statistical Analysis Software (SAS). When I finally got a hang of it, we started all over again with R; your patience and support are beyond belief. Also a big thanks to Roland Valori for sharing your incredible colonoscopy knowledge and effectively pointing out weaknesses and revising proposed papers.

The value of conducting reseach within a good reseach unit cannot be underestimated. The support from the surgical gastroenterology research unit led by by Prof. Ole Thorlacius Ussing has been vital to everyday research life as has support from my fellow PhD students: Sabrina, Simon, Henriette, Rasmus and Sissel. Without you for bounching ideas, overcomming issues and sharing quite a few cups of coffee, PhD life would not have been the same. I also would like to thank Anni for her ability to solve minor and major problems and, finally, Ann and June for help and assistance. The English language support offered by Karina was also highly appreciated.

Three year of PhD studies are not are a quiet time. It is a rollercoaster of conferences, courses, teachings, presentations and shifting obligations; and you come to a point where every thought is about "colonoscopy" and more time is spent at the PhD office than at home. Without devout support from my wonderful girlfriend, Nina, I would never have managed such a project; I'm looking forward to some quiet time with you after this. I'm also grateful for support from my friends and family who still hang around despite being neglected for quite some time. Finally, I would like to mention the never-ending care from my parents, Jan and Hanne Pedersen. You are always there to help and your whole-hearted attempt to fully understand the project is overwhelming. Your care and consideration towards our (soon to be) little family, are endless.

Lasse Pedersen, June 2020

ENGLISH SUMMARY

Colorectal cancer (CRC) is the third most common cancer in Denmark and with almost 5,000 annual cases, the incidence is among the highest in the world. The preferred diagnostic procedure for detecting CRC is colonoscopy, either as a test on symptomatic patients or as a part of a CRC screening programme. Colonoscopy can both diagnose the colorectal cancer and prevent the disease by removal of premalignant lesions. Unfortunately, only little research has been devoted to the study of colonoscopy quality in Denmark compared with other European countries. However, patients undergoing colonoscopy expect that the procedure diagnoses all malignant and premalignant lesions, is carried out by highly qualified endoscopists and has a very low risk of adverse events. The present thesis addresses several key quality indicators related to such expectations.

In Paper I, post-colonoscopy colorectal cancer (PCCRC) was investigated using national registries. The PCCRC rate was significantly higher in Denmark than in Sweden and the English National Health Service. The PCCRC rate was falling over time, indicating better colonoscopy quality. However, the latest available PCCRC rate was still at 7.9% in 2012. Regression analysis found PCCRC to be associated with tumours in the right side of the colon, small tumour size, diverticulitis, ulcerative colitis, hereditary cancers and a high comorbidity index.

In Paper II, we attempted to improve colonoscopy quality at Aalborg University Hospital measured as the cecum intubation rate (CIR) and polyp detection rate (PDR) through training courses. Junior endoscopists were give a module-based 20-day supervised training course, while “up-skill”, polypectomy and train the colonoscopy trainers courses were held for experienced endoscopists. A continuous colonoscopy quality monitoring system was also introduced. Overall, CIR increased significantly from 87.1% to 92.1%. Overall PDR increased from 33.6% to 41.7%, but the increase was not significant in multivariable regression analysis.

In Paper III, we investigated adverse events associated with colonoscopy in the North Denmark Region. Readmission and death were identified using electronic health records and classified, graded and attributed according to the American Society of Gastrointestinal Endoscopy lexicon. Overall, the adverse event rate was 9.9‰. The majority of complications (5.8‰) were related to non-procedure-related events (cardiovascular, pulmonary, thromboembolic, electrolyte imbalance, etc.) rather than to procedure-related (bleeding and perforations) events, which accounted for 4.1‰. Bleeding and perforation rates were within range of other published studies, albeit in the upper interval. Perforation rates were just above or below minimal quality assurance standards set in the UK, but far above proposed aspirational targets.

In Paper IV, we explored the concept of overall and standardized performance indicators (CIR and PDR) through data obtained from the colonoscopy reporting system. Guidelines commonly provide specific performance goals related to colonoscopy indication and gender as these factors can affect the CIR or PDR. However, calculating separate performance goals is tedious, reduces the number of procedures available for assessment and prolongs the observation period needed to obtain reliable performance estimates. Studies finding overall CIR and overall PDR useful have emerged, but validity could be affected by differences in case-mix among endoscopists. We calculated standardized performance indicators that adjust for differences in endoscopist case-mix (colonoscopy indication, patient age and patient gender) and compared them to an overall CIR and overall PDR. Standardization had little effect on CIR with a maximum change in CIR of 1.95 percentage points, interquartile range [0.27-0.86] percentage points and a more pronounced effect on the PDR with a maximum change of 11.21 percentage points, interquartile range [2.05-6.70] percentage points. Overall CIR seems to be a reasonable performance marker, but caution must be taken interpreting performance around minimal acceptable standards. Overall PDR could be misleading in endoscopists with an outlier case-mix. A free R programme to analyse your own colonoscopy database and explore the concept of overall performance markers is available in an open file repository.

In conclusion, this PhD thesis finds that more CRCs are missed or not prevented by colonoscopy in Denmark than in Sweden and in the English National Health Service. This finding seems to correlate with scarce colonoscopy quality improvement initiatives. Endoscopy training programmes and screening certification have not yet been implemented on a national scale. We successfully introduced local training programmes and regional quality monitoring which led to an overall improvement in CIR. Colonoscopy adverse events remain a problem; and the current standard in the North Denmark region corresponds to the minimal acceptable standard set in the UK.

DANSK RESUME

Kræft i tyk- og endetarm (CRC) rammer næsten 5.000 danskere årligt og er dermed den tredje hyppigste kræftform i Danmark. Incidensen af CRC i Danmark er blandt den højeste i verden. Kikkertundersøgelse af tyktarmen (koloskopi) er den fortrukne metode til at diagnosticere CRC. Indikationen for koloskopi er enten som diagnostisk undersøgelse hos symptomatiske patienter (blod i afføringen eller ændret afføringsmønster) eller som led i en screeningsundersøgelse. Ved koloskopi kan CRC diagnosticeres direkte ved at tage biopsier. Det er også muligt at bruge undersøgelsen som forebyggelse ved at fjerne polypper, der udgør forstadier til kræft. For at sikre, at koloskopi er et trygt redskab til diagnostik og forebyggelse af CRC, kan kvaliteten af undersøgelserne måles med forskellige parametre. I Danmark har der desværre ikke været stor opmærksomhed på måling af kvaliteten af koloskopi sammenlignet med fx England. Fra patientens synspunkt må det dog være en naturlig forventning, at undersøgelsen finder alle kræftknuder og forstadier til kræft, at endoskopørerne er dygtige, og at der er lille risiko for komplikationer. Det er baggrunden for denne afhandling, der består af fire studier:

I det første studie undersøgte vi CRC, som blev overset eller ikke forebygget ved koloskopi, kaldet "post-colonoscopy colorectal cancer" (PCCRC). Til dette formål blev der anvendt nationale danske registre. Vi fandt, at PCCRC-raten var signifikant højere i Danmark end i Sverige og National Health Service i England. PCCRC-raten faldt over tid, hvilket indikerede en bedre koloskopikvalitet sidst i studieperioden, men de senest tilgængelige tal fra 2012 viser forsat en PCCRC rate på 7,9%. Vores regressionsanalyse fandt, at PCCRC var associeret med tumorer i højre side af colon, lille tumorstørrelse, divertikulitis, colitis ulcerosa, arvelig cancer og højt komorbiditetsindeks.

I det andet studie så vi på muligheder for at forbedre kvaliteten af koloskopi på Aalborg Universitetshospital gennem træningskurser og målte dette på coecum intubationsraten (CIR) og polyp detektionsraten (PDR). Yngre læger (introduktionsstilling samt første år af hoveduddannelse) gennemgik et 20-dages superviseret træningsprogram, mens en serie af polypektomi- og supervisorkurser blev afholdt for mere erfarne koloskopører. Et monitoreringssystem til kontinuerligt at vurdere koloskopikvaliteten blev ligeledes indført. CIR steg signifikant fra 87,1% til 92,1%. PDR steg fra 33,7% til 41,7%, men stigningen var ikke signifikant i den multivariable regressionsanalyse.

I det tredje studie undersøgte vi risikoen for komplikationer ved koloskopi. Vi analyserede koloskopier udført i Region Nordjylland. Genindlæggelse og død blev identificeret ud fra patientjournaler og herefter klassificeret, graderet og tilskrevet koloskopi i henhold til retningslinjerne fra the American Society of Gastrointestinal Endoscopy. Komplikationsraten ved koloskopi var 9,9‰. De fleste komplikationer

(5,8‰) skyldtes faktorer, der ikke direkte kunne relateres til proceduren (kardiovaskulære, lungemæssige, tromboemboliske, elektrolytubalance, etc.), mens procedurerelaterede faktorer (blødning og perforation af tarmen) udgjorde 4,1 ‰. Niveauet af blødnings- og perforationskomplikationer var sammenligneligt med andre publicerede studier, omend i den øvre del af det forventede niveau. Perforationsraten lå tæt på minimumsstandarderne i de engelske retningslinjer, men langt fra den ønskede standard.

I det fjerde studie undersøgte vi muligheden for at anvende universelle og standardiserende performanceestimater som markør for koloskopikvaliteten (CIR og PDR). Guidelines anvender ofte separate performancemål afhængigt af koloskopi-indikation og køn, da disse faktorer kan påvirke enten CIR eller PDR. Inddeling i disse undergrupper reducerer antallet af procedurer til beregning af de enkelte performanceestimater, udvider konfidensintervallerne og forlænger den nødvendige observationsperiode for at opnå pålidelige performanceestimater. Enkelte tidligere studier har undersøgt universelle performancemarkører og fandt disse anvendelige, men validiteten kan påvirkes af forskelle i case-mix blandt endoskopørerne. Vi beregnede standardiserede performancemarkører, der justerer for forskelle i endoskopørernes case-mix (koloskopiindikation, patientalder og køn) og sammenlignede dem med universelle performancemarkører. Standardisering havde lille effekt på CIR med en maksimal ændring på 1,95 procent point, interkvartilbredde [0,27-0,86] procent point og en større effekt på PDR med en maksimal ændring på 11,21 procent point, interkvartilbredde [2,05-6,70] procent point. En universel CIR kan dermed umiddelbart anvendes som markør for koloskopi-kvaliteten, dog med forsigtighed for endoskopører, der performer tæt på minimal acceptabel standard. En universel PDR kan være vildledende for endoskopører med et specielt case-mix. Vi har udviklet et *R* program til analyse af koloskopidatabaser, der giver mulighed for at undersøge egne universelle performansmarkører, og programmet er frit tilgængeligt.

Denne afhandling beskriver kvaliteten af koloskopi fra fire vinkler. Vores fund indikerer, at flere CRC overses eller ikke bliver forebygget i Danmark sammenlignet med Sverige og England. Den mest oplagte forklaring herpå er manglende kvalitetsforbedringsinitiativer som fx nationale træningsprogrammer og koloskopør-akkreditering samt utilstrækkelig kvalitetsmonitorering. I studiet implementerede vi lokale træningsprogrammer og løbende koloskopikvalitetsmontorering, hvilket øgede andelen af komplette undersøgelser (CIR) signifikant. Komplikationsraten til koloskopi er ca. 1%, blødninger og perforationer forekommer på et niveau svarende til den minimale acceptable standard efter engelske retningslinjer. Der er således god grund til forsat at styrke kvaliteten af koloskopier i Danmark gennem øget uddannelse og monitorering. Trods forbedringer er den nuværende monitorering af koloskopikvaliteten ikke på niveau med anbefalingerne fra European Society of Gastrointestinal Endoscopy eller World Endoscopy Organization.

ABBREVATIONS

95%CI	95% confidence interval
ACE	Assessment of competence in endoscopy
ADR	Adenoma detection rate
AE	Adverse event
APC	Adenomatous polyposis coli
ASGE	American Society for Gastrointestinal Endoscopy
ATC-code	Anatomical Therapeutic Chemical Code
BI unit	Business intelligence unit
CI	Confidence interval
CIMP	CpG island methylator phenotype
CIN	Chromosomal instability
CIR	Cecum intubation rate
CPR	Central Person Registry (personal identification number)
CRC	Colorectal cancer
CT	Computed tomography
DC	Diagnosed cancer
DCR	Danish Cancer Registry / Cancerregisteret
DNPR	Danish National Patient Registry / Landspatientregisteret
DNPreR	Danish National Prescription Registry / Dansk receptdatabase
EHR	Electronic health records
ESGE	European Society of Gastrointestinal Endoscopy
FAP	Familial adenomatous polyposis
FIT	Faecal immunochemical test
GI tract	Gastrointestinal tract
HDI	Human Development Index
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
MEI	Magnetic endoscope imaging
mAPP	Mean adenoma per positive procedure

MMR	Mismatch repair
mPPP	Mean polyp per positive procedure
MSI	Microsatellite instability
NBI	Narrow-band imaging
NHS	National Health Service
NOMESCO	Nordic Medico-Statistical Committee
NRCL	Nurse-reported comfort level
OR	Odds ratio
PCCRC	Post-colonoscopy colorectal cancer
PCCRC-3yr	3-year post-colonoscopy colorectal cancer rate
PDR	Polyp detection rate
PET-CT	Positron emission tomography – computed tomography
PPV	Positive predictive value
PRR	Polyp retrieval rate
RR	Relative risk
SFI	Supplementary files
SSA	Sessile serrated adenomas
TNM	Tumour, Node, Metastasis
UICC	Union for International Cancer Control
UK	United Kingdom
US	United States of America
WEO	World Endoscopy Organization
WHO	World Health Organization
WT	Withdrawal time

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Endoscopy 2019; 51; 733-741.
DOI: 10.1055/a-0919-4803

Paper II **Improving colonoscopy quality through individualized training programmes**
Pedersen L, Bernstein I, Lindorff Larsen K, Green C, Torp-Pedersen C.
Danish Medical Journal 2020; 67(8).
PMID: 32741439.

Paper III **Colonoscopy adverse events: Are we getting the full picture?**
Pedersen L, Sorensen N, Lindorff Larsen K, Green C, Wensel N, Torp-Pedersen C, Bernstein, I.
Scandinavian Journal of Gastroenterology 2020; 55; 979-987.
DOI: 10.1080/00365521.2020.1792541

Paper IV **Colonoscopy: The reliability of overall cecum intubation rate and overall polyp detection rate as performance indicators**
Pedersen L, Bernstein I, Lindorff Larsen K, Green C, Gerds T A, Torp-Pedersen C.
In draft

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CHAPTER 1: INTRODUCTION

1.1. PREFACE

The idea for this PhD emerged in late 2014 and early 2015 when the world was in a different place, at least from a Danish colonoscopy quality viewpoint. The Danish colorectal cancer (CRC) screening programme had just been initiated, but results had not yet been published. Results were anxiously anticipated as very little was known about Danish colonoscopy quality because colonoscopy quality had not been measured on a large scale. The lack of quality data was accompanied by a scarcity of formal training as a two-day simulator course was the only available training option. By tradition, the Danish colonoscopy service is primarily provided by surgeons, whereas common practice in most European countries and the United States of America (US) is that gastroenterologists perform the majority of procedures.

The concept of "colonoscopy quality" evolved quickly after the millennium. The US multi-society task force on colorectal cancer published their *"Quality in the Technical Performance of Colonoscopy and the Continuous Quality Improvement Process for Colonoscopy"* in 2002, setting a list of specific goal and recommendations for colonoscopy quality and monitoring.[1] The US was not the only country driving colonoscopy quality forward. In England, concerns were raised about colonoscopy quality, and a nationwide colonoscopy survey was carried out. The study published in 2004 found appalling results with a very high number of incomplete procedures and inadequate training programmes.[2] The study led to massive quality improvement initiatives with accreditation, individual performance monitoring and training programmes. The effect was remarkable. A new nationwide survey published in 2013 by Gavin et al. found massive improvements.[3] The concept of colonoscopy training and accreditation did not evolve in Denmark, and the Danish CRC screening programme was introduced in 2014 without any formal requirements for screening endoscopists. The Danish CRC screening programme tracked performance indicators on a hospital level and introduced the concept of performance monitoring to many Danish endoscopists. Whether the screening programme or mounting evidence of quality improvement outside Danish boundaries was the main driving force is unknown, but interest in colonoscopy quality began to rise, also in the North Denmark Region.

Initially, our main focus was to create colonoscopy training courses for junior doctors. During the first year of surgical training, a colonoscopy training programme could consist of six partly supervised training days scattered over a one-year period. It was a nuisance to junior doctors, supervisors and patients alike. It did not take long to realize that the need for proper training might extend beyond junior doctors. Some "experienced" endoscopists seemed to have a disproportionate amount of incomplete procedures. However, separating a bad streak of colonoscopies and consistent inferior

performance is difficult without an endoscopist monitoring system; the need for such a system was apparent.

An important part of monitoring quality is to monitor complications. Unfortunately, we had seen cases of severe adverse events (AEs) related to colonoscopy. Some were caused by perforations; others were related to cardiac arrhythmias. Colonoscopy AEs had never been examined in a Danish context, and we were keen to investigate the full range of potential AEs and to compare Danish rates to rates reported in other studies and mentioned in guidelines.

From a patient perspective, pain, incomplete procedures and AEs sounds bad enough; but if at least all possible CRCs are identified or prevented, the procedure might be tolerable. Unfortunately, studies on CRC occurring shortly after colonoscopy were published, revealing that cancers or precancerous lesions were likely missed.[4–8] Using the extensive Danish national registries to compare Danish numbers of missed cancers with those reported for other countries therefore became a priority.

Guidelines often recommended different colonoscopy performance targets for specific subgroups as several factors can affect the chance of intubating the cecum or finding polyps.[9–11] However, setting different performance targets for subgroups widens confidence limits to a degree where performance monitoring becomes almost useless on the individual endoscopist level. We hence decided to calculate standardized performance markers and investigate the effect of standardization compared to simple, overall performance markers (CIR and PDR).

This thesis covers four aspects of colonoscopy quality. It offers a national perspective on CRC occurring shortly after colonoscopy (Study I), a local perspective to improve colonoscopy training, quality monitoring and colonoscopy quality (Study II), a regional perspective on colonoscopy AEs (Study III) and a new perspective on colonoscopy performance indicators (Study IV).

Chapter 1 offers a short introduction to many aspects of the subject necessary to understand this PhD thesis. For experienced endoscopists, the terminology and information in this chapter will be familiar; however, for physicians and non-medical personnel unfamiliar with colonoscopy, it provides basic information. Chapters 2 and 3 specify the precise aims and methodology used in the PhD thesis and related papers. Chapter 4 gives a summary of the results of the four studies and relevant results not included in the published papers. Chapter 5 covers a general discussion followed by conclusion and perspectives in chapter 6 and 7, respectively. Published papers and paper drafts are found in the last section of this thesis.

1.2. ANATOMY OF THE LARGE INTESTINE

The gastrointestinal tract (GI tract), strecthing from the oral cavity to the anal verge, is generally divided into the upper and lower GI tract. The upper GI tract reaches from the oral cavity to the duodenum. Its primay function is transportion of the swallowed food bolus and enzymatic digestion. The lower GI tract consists of the small and large intestine. The function of the small intestine (jejunum and ileum) is primarily absorption of nutrients, while the large intestine (the colon) handles water reabsorption and propels the excess waste (feces) for elimination. The colon can be divided into several subsegments as seen below:

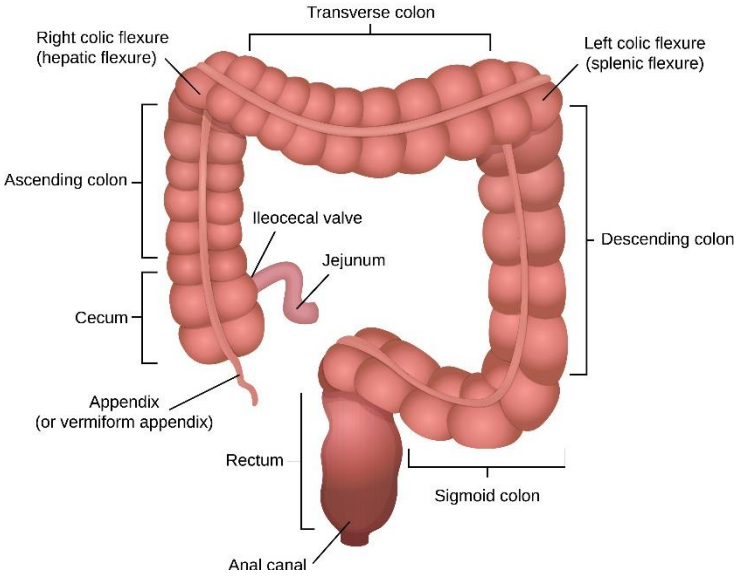

Figure 1 Anatomy of the colon with sub segments

Some parts of the colon are relatively fixed, while others remain highly mobile. The rectum is bound to the pelvic floor and fixed, while the sigmoid colon has a long mesocolon that makes it highly mobile. Ligaments bind the left and right colonic flexure to adjacent structures, but the transverse colon connecting the flexures is highly mobile with a wide mesocolon. The ascending and descedning colon are retroperitoneally located or with a narrow mesocolon, giving them a relatively fixed position. The cecum is located intraperitonenally and is usually relativelly mobile.

The total length of the colon is approx. 1 metre with a wall thickness of 0.2-0.4 cm, thickest in the sigmoid colon with gradual thinning towards the cecum.[12] The colon wall concists of the mucosa (an inner epihetlial layer, the lamina propria and the

muscolaris muscosae), the submucosa, the muscularis layer (with a circular and longitudinal muscle layer) and the serosa:

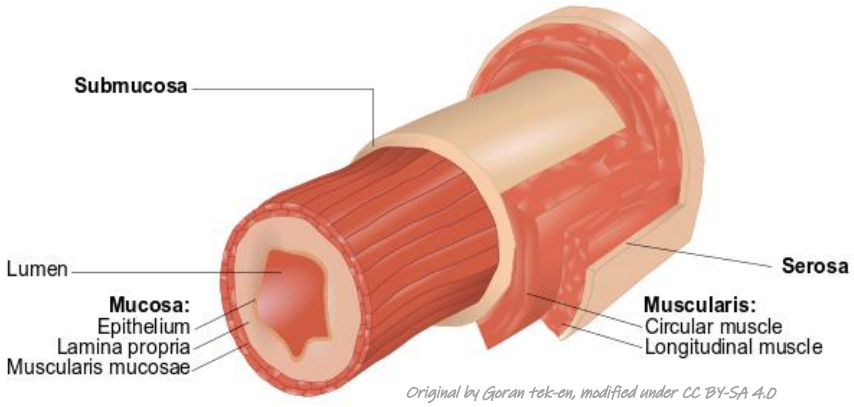

Figure 2 Anatomy of the colonic wall

1.3. THE ADENOMA-CARCINOMA SEQUENCE

The majority of CRCs is believed to originate through the andenoma-carcinona sequence first described by Vogelstein et al. in 1988.[13,14] Over time, genomic alteration in the mucosal epithelial cells occurs, affecting oncogenes and tumour suppressor genes. The result is a growth advantage and the formation of an adenoma. As mutations increase, so do the growth rate and the amount of dysplasia until a malignant polyp and, finally, cancer is the result. A typical CRC has 33-66 gene mutations.[15] Under normal circumstances, the adenoma-carcinoma sequence is a slow process. The timeframe is estimated to be 10.6-25.8 years.[16]

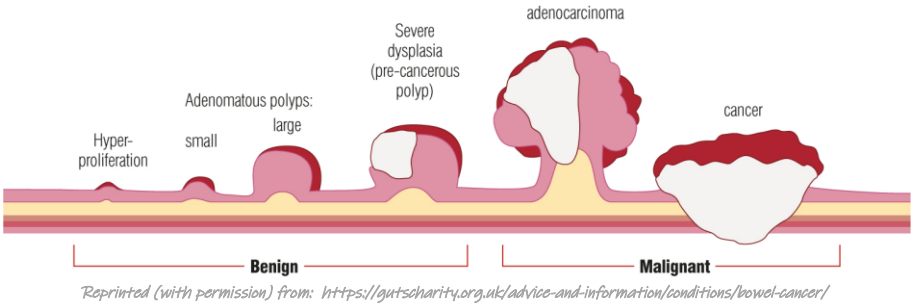

Figure 3 The adenoma carcinoma sequence

Tumour biology may play an important role in development of CRC; at least three predominate pathways are known: the chromosomal instability (CIN) pathway, the mismatch repair (MMR) pathway and the serrated pathway.[17] The CIN pathway and the MMR pathway are generally considered mutually exclusive, while the serrated pathway can occur together with the two other pathways.[18,19]

1.3.1. THE CIN PATHWAY

The CIN pathway is the most common pathway, and it is observed in 80% of CRC.[20] It is a result of genetic mutations related to the adenomatous polyposis coli (APC) tumour suppressor gene, the K-ras oncogene and the p53 tumour suppressor gene. Germline mutations in the APC gene are responsible for the disease known as familial adenomatous polyposis (FAP), where hundreds of polyps develop in the colon, inevitably leading to CRC at the age of 35-40 if untreated.[21,22]

1.3.2. THE MMR PATHWAY

Microsatellites are a sequence of tandem repeats (1-5 base pairs) that are repeated many times. They are abundant throughout the human genome and are prone to errors during DNA replication. Errors are usually corrected by MMR proteins. However, if MMR proteins become incompetent, microsatellite errors accumulate to a state called microsatellite instability (MSI).[21] The Lynch syndrome is characterized by a germline mutation in the MMR proteins that greatly increases the risk of CRC and other cancers. Lynch syndrome accounts for approximately 3% of CRC, while MSI is found in around 15% of sporadic CRC.[23] The duration of the adenoma-carcinoma sequence is rapidly increased in patients with Lynch syndrome. The mean time is estimated to be three years.[24] MSI is associated with an increased risk of post-colonoscopy colorectal cancer (PCCRC) among sporadic CRC cases.[25–27]

1.3.3. THE SERRATED PATHWAY

Sessile serrated adenomas (SSAs) have a flat non-polypoid appearance that is distinctive from that of polypoid polyps as seen in Figure 3. SSAs are thought to develop from defects in methylation known as CpG island methylator phenotype (CIMP), a pathway first described by Toyota et al. in 1999.[28] Their macroscopic appearance resembles that of benign hyperplastic polyps, and their flat appearance makes them more difficult to detect and remove.[17] SSAs occur predominantly in the right side of the colon. CIMP is associated with PCCRC.[18]

1.4. COLORECTAL CANCER EPIDEMIOLOGY

CRC is the third most common cancer in the world with over 1.8 million new cases and 881,000 deaths in 2018.[29] The incidence differs much between countries with a 6-to-8-fold variation. CRC can be considered a marker of socioeconomic development.[29,30]

Higher CRC incidence is present among countries with higher Human Development Index (HDI) score, a combined score of life expectancy, schooling and income. Whenever a country experienced rapid socioeconomic improvements, the CRC incidence tended to rise with higher HDI.[29] Changes in population demography and socioeconomic growth are likely to see an increasing number of CRC cases in the future. It is estimated that 2.4 million annual CRC cases will occur world wide by 2035.[31]

Like most other Western countries, Denmark has a high incidence of CRC of around 80 per 100,000 person years.[32] The annual number of cases spiked in 2014 with more than 5,000 new cases.[32] As seen from Figure 4, the sharp rise in the number of cases in 2014 coincides with the introduction of the Danish CRC screening programme.[33–35] Since 2014, the annual number of new Danish CRC cases has declined, most likely due to lead time bias. In other high-HDI countries such as the US, the CRC age-standardized incidence has been declining in individuals > 50 years old for more than 20 years, but with an increasing incidence among individuals < 50 years old.[36] The incidence of CRC among young individuals is increasing in Denmark as well.[37,38] In the US, colonoscopy screening programmes were introduced earlier, but they are unlikely to fully explain the declining incidence among older individuals.[39]

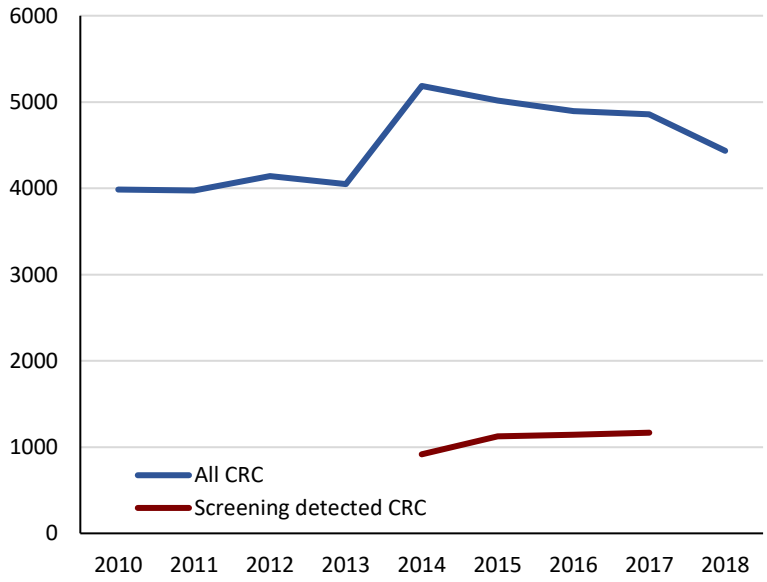

Figure 4 Individuals diagnosed with CRC in Denmark from 2010-2018

Note: Complete numbers of screening-detected CRC from 2018 are unavailable due to incomplete data.

1.5. CRC DIAGNOSIS, STAGING AND PROGNOSIS

Colonoscopy remains the gold standard for investigating the colon for pathology such as CRC and to perform preoperative histological verification of the disease.[40] Colonoscopy may be performed for various indications but is commonly part of a screening programme or diagnostic procedure performed due to lower-GI bleedings, anaemia or a change in bowel habits. Modern image modalities such as positron emission tomography – computed tomography (PET-CT) or regular computed tomography (CT) conducted for other reasons than CRC often give rise to suspicious colonic findings warranting a subsequent colonoscopy.

CRCs in Denmark are classified according to the Tumour, Node, Metastasis (TNM) classification system of the Union for International Cancer Control (UICC). The TNM classification describes the size and/or extension of the primary tumour (T), the degree of spread to regional lymph nodes (N) and presence of distant metastasis (M). The anatomical extent of the CRC is grouped in stages according to survival. Stage I has a 5-year relative survival comparable to that of the rest of the population, whereas only 15-20% of individuals with Stage IV CRC are alive after 5 years in Denmark.[41] The TNM classification is updated regularly; the 8th edition is found in Table 1.[42] The TNM classification replaced the Dukes classification used in Denmark until 2003.[43]

Table 1 The TNM classification system and staging (8th edition) with Danish 5-year relative survival according to UICC stage.

T: Primary tumour	
Tis	Superficial tumour without extension through the muscularis mucosae
T1	Tumour invades submucosa
T2	Tumour invades the muscularis layer
T3	Tumour invades through the muscularis layer into the subserosa
T4a	Tumour growth through the serosa layer but not into nearby tissue/organs
T4b	Tumour growth through the serosa layer and into nearby tissue/organs
N: Regional lymph nodes	
N0	No spread to regional lymph nodes
N1a	Tumour cells found in 1 regional lymph node
N1b	Tumour cells found in 2 or 3 regional lymph nodes
N1c	Nodules made up of tumour cells found in the structures near the colon that do not appear to be lymph nodes
N2a	Tumour cells found in 4 to 6 regional lymph nodes
N2b	Tumour cells found in 7 or more regional lymph nodes
M: Distant metastases	
M0	No spread to a distant part of the body
M1a	Cancer spreading to 1 other part of the body beyond the colon/rectum
M1b	Cancer spreading to > 1 part of the body other than the colon/rectum
M1c	The cancer has spread to the peritoneal surface.

Anatomical stage					
	T	N	M	5-year relative survival	
				Colon (%)	Rectum (%)
Stage 0	Tis	N0	M0	-	-
Stage I	T1,T2	N0	M0	101	98
Stage II	T3,T4	N0	M0		
Stage IIA	T3	N0	M0	89	88
Stage IIB	T4a	N0	M0		
Stage IIC	T4b	N0	M0		
Stage III	Any T	N1,N2	M0		
Stage IIIA	T1,T2	N1	M0		
	T1	N2a	M0		
Stage IIIB	T1,T2	N2b	M0		
	T2,T3	N2a	M0	73	80
	T3,T4a	N1	M0		
Stage IIIC	T3,T4a	N2b	M0		
	T4a	N2a	M0		
	T4b	N1,N2	M0		
Stage IV	Any T	Any N	M1		
Stage IVA	Any T	Any N	M1a	15	20
Stage IVB	Any T	Any N	M1b		
Stage IVC	Any T	Any N	M1c		

1.6. THE ENDOSCOPE: HISTORY, FUNCTIONS AND ADJUNCTS

Development of the modern endoscope began in the late 1950s and early 1960s with the invention of flexible glass fibres. The first snare polypectomy was performed by Shinya and Wolff in 1971.[44] In the early days, the endoscopist had to look directly through a lens into the endoscope. This changed with the introduction of the video scope in 1983.[45] Since then, flexibility, optic resolution and endoscopic tools have vastly improved. A modern endoscope for examining the colon (a colonoscope) consists of the flexible tube for insertion into the colon, a scope handle with wheels and buttons for tip control, insufflation, suction and washing the lens. A working channel is available to insert tools for polyp removal and biopsies. An umbilical cord runs from the scope handle to the rack. The rack controls endoscope brightness, settings for cutting and haemostasis and outputs for the video monitor. Two additional adjuncts are commonly used: narrow-band imaging (NBI) and magnetic endoscope imaging (MEI). NBI consists of a series of filters that are applied to the endoscopic image to enhance contrast and visibility of the vascular pattern for better adenoma diagnosis.[46] The MEI provides a real-time presentation of the actual form and positioning of the scope through electromagnetic coils embedded within the endoscope. Information on scope form and positioning is helpful to achieve higher CIR, shorter cecum intubation time and less patient pain.[47] Recent advances in colonoscopy include artificial intelligence to detect polyps.[48]

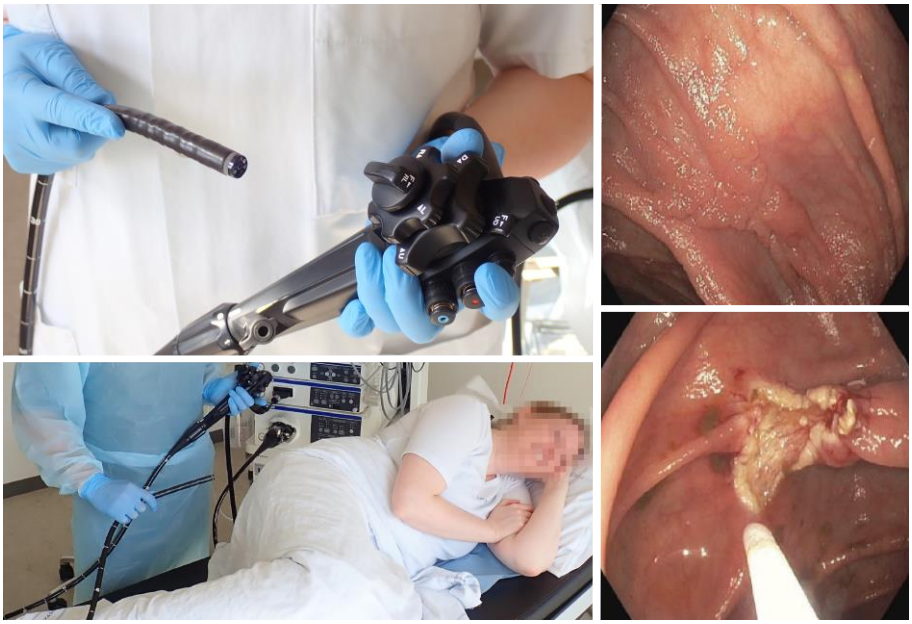

Figure 5 The colonoscope and endoscopic polyp removal

Top left: The colonoscope tip, controls and working channel. Bottom left: Initiation of a colonoscopy in the left side position. Top right: A 15 mm flat polyp. Bottom right: Polyp site after hot snare polypectomy.

1.7. KEY PERFORMANCE INDICATORS

Key performance indicators reflect a number of performance markers that can be used to monitor colonoscopy quality at an individual endoscopist, department or national level. A short introduction to performance markers used in this PhD thesis follows below:

Cecum intubation rate (CIR)

CIR is calculated by the number of procedures where the cecum is reached divided by the number of procedures performed. It is a commonly used performance marker endorsed by major gastrointestinal societies and guidelines.[49–52] The minimum acceptable CIR is usually 90-95%. Ambiguity still exists on requirements for documentation and potential adjustments. UK guidelines require photographic proof that the cecum has been reached, while the Danish CRC screening programme relies on a "complete colonoscopy" at the endoscopist's discretion.[34,50] In studies related to this thesis, cecum intubation was based on the endoscopist's documentation of *intubation* of the small intestine or ileocolic anastomosis or *visualization* of the ileocecal valve, triradiate fold or the appendix orificium. The requirements are identical to those in the UK national quality audit from 2012.[3] Adjustments of CIR

are sometimes performed to exclude certain cases (for instance cases with bad bowel preparation). In this thesis, CIR was calculated according to the European guidelines where only malignant stenosis is excluded.[49]

Polyp detection rate (PDR)
The PDR is defined by the percentage of colonoscopies where at least one polyp is found. The definition of a polyp is at the endoscopist's discretion. The PDR is believed to be a good marker of the adenoma detection rate (ADR).[53–55] The PDR has also been directly linked to the PCCRC rate.[56]

Polypectomy rate
The polypectomy rate is similar, though not identical, to the PDR. A polyp is usually removed upon detection; however, anticoagulant treatment or complex polypectomies might postpone removal for a later procedure. Polypectomy is usually coded as a procedure code or a billing code allowing for retrospective data analysis. The polypectomy rate has been inversely linked to the risk of PCCRC.[57,58]

Adenoma detection rate (ADR)
The ADR is defined by the percentage of colonoscopies where at least one adenoma is found. The ADR is different from the PDR as only histologically verified adenomas are included. A high ADR has been linked to a lower risk of PCCRC.[59,60]

Mean polyp/adenoma per positive procedure (mPPP/mAPP)
Mean polyp per positive procedure (mPPP) refers to the number of polyps found per procedure if at least one polyp is found. mAPP is similar to mPPP but only counts verified adenomas.

Withdrawal time (WT)
Refers to the time spent withdrawing the scope from the cecum to the anal verge. WTs of more than 6-10 minutes are associated with higher PDR/ADR and PCCRC.[61,62] Only procedures without endoscopic interventions are counted when measuring WT. When measuring WT in this PhD, colonoscopies with polypectomies or biopsies due to suspected inflammatory bowel disease (IBD) or CRC are excluded.

Polyp retrieval rate (PRR)
PRR refers to the percentage of removed polyps that are retrieved and sent for pathological examination. UK guidelines set a PRR target of > 90%.[50]

Post-colonoscopy colorectal cancer rate (PCCRC rate)
PCCRC refers to CRC that occurs shortly after a negative colonoscopy (a colonoscopy without a malignant finding). The term interval CRC is sometimes used interchangeably but refers to a scheduled follow-up, which might not always be the case. The timeframe for investigating PCCRC when calculating rates is usually 3

years and referred to as the PCCRC-3yr rate. The PCCRC-3yr rate is usually calculated by:

$$\text{PCCRC} - 3\text{yr} = \frac{\text{PCCRC}}{\text{PCCRC} + \text{DC}}$$

where *PCCRC* is the number colonoscopies with a CRC occurring 6-36 months after colonoscopy and *DC* (diagnosed cancers) is the number of colonoscopies with a CRC from 0-6 months after colonoscopy.[63,64]

Number of colonoscopies

A high procedure volume per endoscopist does not necessarily reflect competence; however, a number of initial procedures are needed to learn the procedure and a certain number of annual procedures is necessary to stay familiar with the procedure. Studies suggest that it takes 175-500 procedures to become competent in colonoscopy.[65–68] Guidelines recommended a minimum of 100-300 procedures per year for each endoscopist.[49,50] Studies have found associations between endoscopist volume and the PCCRC rate.[58,69]

Nurse-reported comfort level (NRCL)

NRCL also known as the Gloucester Comfort Score measures the patient's discomfort on a level from one to five.[3,70] The attending nurse judges the patient's experience by the severity and frequency of pain. A score of three or less is generally considered acceptable. A description of the NRCL is found in Table 2. It has been speculated that isolated focus on performance indicators such as CIR could cause some endoscopists to exert additional force (and discomfort) to reach the cecum. Evidence so far does not support this thesis as higher CIR and higher PDR rates are associated with lower NRCL scores.[70]

Table 2 Nurse-reported comfort levels of 1-5 with definitions

1. Comfortable: Talking/comfortable throughout
2. Minimal: One or two episodes of mild discomfort without distress
3. Mild: More than two episodes of mild discomfort without distress
4. Moderate: Significant discomfort experienced several times with some distress
5. Severe: Frequent discomfort with significant distress

Adverse event rate

Colonoscopy is not a risk-free procedure as it carries risks for morbidity and mortality. AEs can by procedure related (perforation and bleedings) or non-procedure related (cardiovascular, dehydration, electrolyte disturbance, etc.). Timeframes and methods for investigating AEs are variable, making them difficult to compare.[49,71,72] Continuous tracking of AEs is recommended by major guidelines and societies.[9,49,73]

1.8. COLONOSCOPY IN DENMARK

The annual number of colonoscopies in Denmark has increased from around 20,000 procedures in the year of 2000 to almost 120,000 procedures in 2018. The vast majority of procedures including screening are performed in surgical gastroenterology units. By 2018, 86% of procedures were performed in surgical gastroenterology units and 8% in gastroenterology units.

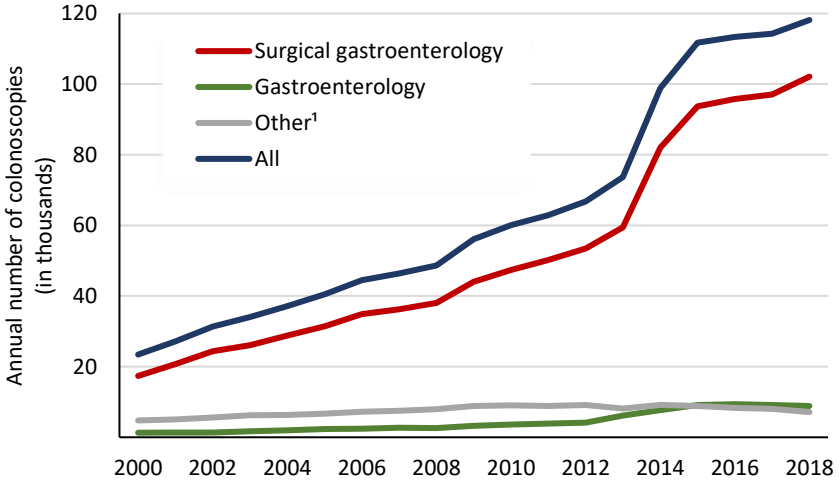

Figure 6 Number of annual colonoscopies performed in Denmark from 2000-2018 according to specialty.

[1]Other: All other fields of specialty and not specified. Source: DNPR (section 1.9 and section 3.1).

The situation is different from that of other European countries and the US where the proportion of colonoscopies performed by gastroenterologists is higher than in Denmark.[3,74,75] At present, there are no national Danish colonoscopy accreditation, certification or training programmes beyond 1-2-day courses for physicians, but surgical gastroenterology trainees are required to do 200 colonoscopies during their 5-year training programme. As demand for colonoscopies increased, a national (colonoscopy) training programme for nurses was established in 2011. This programme certifies nurses to perform colonoscopies with polypectomies up to 10 mm. The programme has a theoretical and practical part with 150 supervised colonoscopies to be completed within one year.[76] Certified colonoscopy nurses are required to do 100 colonoscopies / year to remain active. Currently, > 50 certified colonoscopy nurses are active in Denmark.

Individual endoscopist performance monitoring has not been implemented at a national level in Denmark. There is no national database such as the UK National Endoscopy Database or multicentre database comparable to the Norwegian

Gastronet.[77,78] Regional activities to measure individual endoscopist performance indicators have been initiated in the Central Denmark Region.[79]

1.8.1. THE DANISH CRC SCREENING PROGRAMME

The Danish CRC screening programme was introduced in March 2014.[34] The programme covers all Danish citizens who are 50-74 years old. Screening of the primary cohort was completed in 2017. Since then, all citizens in the cohort are offered screening every two years. Individuals are invited by mail with an invitation letter, an information leaflet and the faecal immunochemical test (FIT). Returned FITs are analysed using the OC Sensor (Eiken Chemical Company, Tokyo) with a cut-off of 100 µg haemoglobin/L corresponding to 20 µg haemoglobin/g faeces.[80] Positive FITs are referred for colonoscopy. If the colonoscopy is performed, there are five possible outcomes: CRC, high-risk adenoma, middle-risk adenoma, low-risk adenoma or clean colon.[34,80] Risk assessment is seen in Table 3. In case of a clean colon, the citizen will be invited for FIT again after 8 years.

Table 3 Risk assessment according to colonoscopy findings in the Danish CRC screening program

Low risk	Medium risk	High risk
< 3 adenomas Adenoma size < 10 mm Low-grade neoplasia Tubular adenoma	3 or 4 adenomas Adenoma size ≥10<20 mm High-grade neoplasia Tubulovillous adenoma Villous adenoma	≥ 5 adenomas Adenoma size ≥ 20 mm
Follow-up Biennial FIT screening	**Follow-up** Colonoscopy in 3 years	**Follow-up** Colonoscopy in 1 year

Participation in the Danish CRC programme has been good with 61% returning the FIT test in 2017.[34] This is above the 45% minimum standard set by European guidelines, but below the desired goal of 65%.[81] The FIT was positive in 6.9% of individuals and a subsequent colonoscopy was performed in 90% of FIT-positive individuals. A CRC was detected in 5.9% of colonoscopies. Annually detected CRC in the Danish screening programme can be seen in Figure 4.

Overall, CIR in the Danish CRC screening programme was low in 2017 (84%), but this is mainly due to registrations issues related to the introduction of a new electronic health record (EHR) system in the capital region. The range in CIR among hospitals outside the capital region was 83-95%. ADR varied from 27-67% among hospitals.[34] Currently, the Danish screening programme measures performance indicators at a hospital level, not at an individual endoscopist level.

1.9. DENMARK: HEALTH CARE, REGISTRIES AND THE NORTH DENMARK REGION

The Danish healthcare system builds on a universal, free-for-all, public healthcare system with very little room for private practice. Combined with a long-lasting tradition for national registries, this provides ample opportunities for complete and extensive registry studies. The Danish Cancer Registry (DCR) dates back to 1942 with mandatory reporting since 1987. It covers all cancer diagnosis based on the International Classification of Diseases, 10th Edition (ICD-10) diagnosis, date of diagnosis, disease stage and pathology.[43] The Danish National Patient Registry (DNPR) was established in 1977 and covers admissions to Danish hospitals and outpatient units related to diagnoses, treatments and examinations.[82] The Danish National Prescription Registry (DNPreR) dates back to 1994 and covers all filed prescriptions with dates, product name, World Health Organization Anatomical Therapeutic Chemical Code (WHO ATC code) and packet size.[83]

Another Danish feature is the unique personal identification number (CPR number) assigned to each Danish individual upon birth or immigration. The CPR number is non-replaceable and follows you for life. Every registration in national registries is based upon the CPR number and allows for linkage between multiple registries.

1.9.1. THE NORTH DENMARK REGION

Danish health service is divided into five administrative regions: The North, Central, Southern, Zealand and Capital Region. The North Denmark Region is the smallest of the five regions with 589,000 inhabitants. Colonoscopies are performed at five locations as seen below:

Figure 7 Endoscopy units in the North Denmark Region

Aalborg University hospital covers the main hospital in Aalborg and a satellite unit in Hobro. Thisted became a part of Aalborg University hospital in mid 2018; however, for consistency Thisted is not included when referring to Aalborg University hospital in this PhD. The North Denmark Regional hospital covers the main hospital in Hjørring and a satellite unit at Frederikshavn. Endoscopy units in Frederikshavn, Hobro and Thisted are outpatient endoscopy units, while Aalborg and Hjørring have both surgical and gastroenterology departments.

1.10. SUMMARY AND RESEARCH GAP

Demand for colonoscopies has increased in Denmark during the past 20 years with surgeons performing the majority of procedures. Little attention has been paid to quality monitoring and endoscopist training, which might affect the quality of colonoscopy. This PhD thesis investigated colonoscopy quality from four different perspectives: A national perspective on PCCRC, CRC occurring shortly after colonoscopy (Study I); a local perspective to improve colonoscopy training, quality monitoring and colonoscopy quality (Study II); a regional perspective on colonoscopy AEs (Study III); and a new perspective on colonoscopy performance indicators (Study IV).

The national perspective focused on CRC occurring shortly after colonoscopy, measured by PCCRC rates. PCCRC rates have been investigated in previous studies. Unfortunately, previous publications relied on their own unique methods that were difficult to compare due to differences in patients' populations, timeframes, exclusion criteria and the calculation of the rate itself. Without a comparable method, it is difficult to compare the effect of nationwide colonoscopy quality improvements programmes and to compare rates between different countries and jurisdictions. Danish registries provide a unique opportunity to calculate rates using multiple methods for direct comparison. The World Endoscopy Organization (WEO) published their consensus statement for PCCRC in 2019 while we were preparing our paper for publication.[64] Hopefully, the WEO consensus statement will serve as the future reference for calculating PCCRC-3yr rates. We were quick to adopt the methodology in our paper. Studies related to associations with PCCRC have been examined previously, but not using the vast variables made possible with Danish national registries.[58,63,84–86]

The local perspective focused on colonoscopy training and quality monitoring in an attempt to improve colonoscopy quality. One of the first guidelines recommending individual endoscopist performance tracking was issued by Rex et al. in 2002.[1] Since then, multiple guidelines related to colonoscopy quality assurance and performance monitoring have been published by the European Union, the UK, the US and the European Society of Gastrointestinal Endoscopy **(**ESGE).[49–52] However, when this PhD thesis was initiated, the colonoscopy quality in the North Denmark Region was largely unknown and endoscopists were unfamiliar with the concept of individual

performance monitoring. Similarly, colonoscopy training programmes were restricted to a 2-day simulator course for junior doctors. There was therefore an urgent need for training programmes for both junior and experienced endoscopists and for a colonoscopy quality monitoring system.

The regional perspective focus on complications related to colonoscopy occurring within the North Denmark Region. Colonoscopy complications have been investigated previously in several studies, but ambiguity exists on how to identify AEs; other ambiguities are due to variation in follow-up time (3-30 days).[49,50,72,87] As training and attention to colonoscopy quality have been low in Denmark, we feared that complications might be above the proposed thresholds.[50] In 2017, colonoscopy AEs were validated in the Danish screening programme.[88] The screening programme relies on positive reporting of complication codes; however, when investigating EHRs, a review reported AE rates rising from 0.23% to 0.71%. The review included medical complications. However, according to the validation study, only 3 in 14,671 colonoscopies suffered a medical complication. It seemed like a low number since we had observed both cardiac arrest and hypovolemia related to colonoscopy at Aalborg University Hospital. The need to investigate colonoscopies outside the screening programme and for a wider approach to capture additional complications was apparent. The American Society for Gastrointestinal Endoscopy (ASGE) has published their lexicon on colonoscopy AEs, which could be an effective tool to investigate the full range of AEs.[72]

The new perspective on performance indicators relate to the use of overall performance markers and standardized performance markers. CIR and PDR/ADR are affected by multiple factors such as patient age, patient sex and colonoscopy indication; thus, separate performance goals for subgroups are commonly provided.[10,11,89] Calculating performance goals for subgroups reduces the number of procedures available for assessment, thus widening confidence limits and prolonging the observation period to obtain reliable results. An alternative approach of applying overall CIR and overall PDR comes with a risk as some endoscopists might be unfairly suspected of inferior performance due to a difficult case-mix. The concept has been explored in few previous studies. Rex et al. studied the use of overall ADR and the effect on changes in relation to the minimum acceptable threshold, while Hoff et al. studied CIR in clinical vs screening colonoscopies.[90,91] Both studies found that overall CIR and overall ADR were useful, but generalizability is difficult to evaluate as the setup in relation to endoscopy units, patient population and definition of screening procedures varies between countries and jurisdictions. Standardized performance markers that adjust for differences in case-mix might be an alternative, both as a standalone marker and as a tool to investigate the effect of differences in case-mix. Additional studies are needed to clarify the reliability of overall performance markers and a universal method to investigate the effect of differences in case-mix is warranted.

CHAPTER 2: AIMS

The exact aims of each study related to the four aspects of colonoscopy quality are found below:

Study I: *Danish PCCRC-3yr rates and factors associated with PCCRC*

- Calculate Danish PCCRC-3yr using identical methods previously published from Sweden and the English NHS to allow direct comparison
- Calculate Danish PCCRC-3yr using the WEO consensus method
- Identify factors associated with PCCRC in a Danish setting.

Study II: *Improving colonoscopy quality through individualized training programmes*

- Establish local baseline colonoscopy performance (based on CIR and PDR) before initiating quality improvement initiatives (2015)
- Introduce colonoscopy training programmes for junior and experienced endoscopists
- Implement individual colonoscopy performance monitoring in the North Denmark Region
- Measure the overall effect of training programmes using the performance monitoring system (based on CIR and PDR) in 2019
- Compare performance indicators in the North Denmark Region to UK quality assurance standards.

Study III: *Colonoscopy AEs in the North Denmark region.*

- Investigate the *full* range of potential colonoscopy AEs using a standardized reporting system
- Compare AE rates with previously published studies and UK quality assurance standards
- Identify factors that could help reduce future colonoscopy AEs.

Study IV: *Overall and standardized performance indicators*

- To calculate standardized performance markers based on CIR and PDR that adjust for colonoscopy indication and patient demographics.
- To assess individual endoscopist performance using overall performance markers vs standardized performance markers.
- To develop a generic R programme that can be used to generate performance benchmarks and test the validity of overall performance markers on any colonoscopy database.[92]

CHAPTER 3: METHODS

This section describes the methods used in this PhD in a broader perspective related to national registries, the quality monitoring system, colonoscopy training programmes, data sources, statistics and ethical considerations. A paper has either been published (study I, study II and study III) or drafted (study IV) in relation to each study.[74,93,94] Further details are available within each paper.

3.1. STUDY I: DANISH PCCRC-3YR RATES AND FACTORS ASSOCIATED WITH PCCRC

Study I is based on three Danish national registries: The DCR, DNPR and DNPreR (section 1.9).[43,82,83] A master dataset covering all CRC and colonoscopies from 1 January 1998 to 31 December 2015 was created by searching the DCR and DNPR. CRC was identified using Danish ICD-10 (DC18-DC20) codes, while colonoscopies were identified using the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedure codes: KUJF32 and KUJF35.[95] A comorbidity database was constructed from the DNPR with comorbidities diagnosed until 31 December 2015. Crohn's disease, ulcerative colitis and diverticulitis were defined as in the Danish version of the ICD-10: DK50, DK51 and DK57, respectively. Hereditary CRC was defined as one of the following Danish ICD-10 codes: DZ848A1 – familial history of hereditary nonpolyposis CRC, DZ800 – familial history with cancer in the GI tract, DD126B – hereditary polyposis coli or DD126F - familial adenomatous polyposis. Only comorbidities diagnosed at the time of colonoscopy were used for further analysis. The Charlson Co-morbidity Index was calculated based on ICD-10 codes as defined by Quan et al. one year prior to date of colonoscopy.[96,97] Uncomplicated diabetes (a part of the Charlson Co-morbidity Index) is usually treated by general practitioners. Data from general practitioners are not reported to the DNPR. The DNPreR was searched for ATC code: A10 - drugs to treat diabetes. If a prescription was identified within one year prior to colonoscopy, a positive diabetes diagnosis was assigned.

3.2. STUDY II: IMPROVING COLONOSCOPY QUALITY THROUGH INDIVIDUALIZED TRAINING PROGRAMMES

The Aalborg University colonoscopy quality baseline was established in 2015 by a paper-based survey. Training programmes for experienced and junior endoscopists were subsequently developed. The new 2019 performance baseline was established by the newly developed quality monitoring system. Figure 8 found below provides an overview of the process:

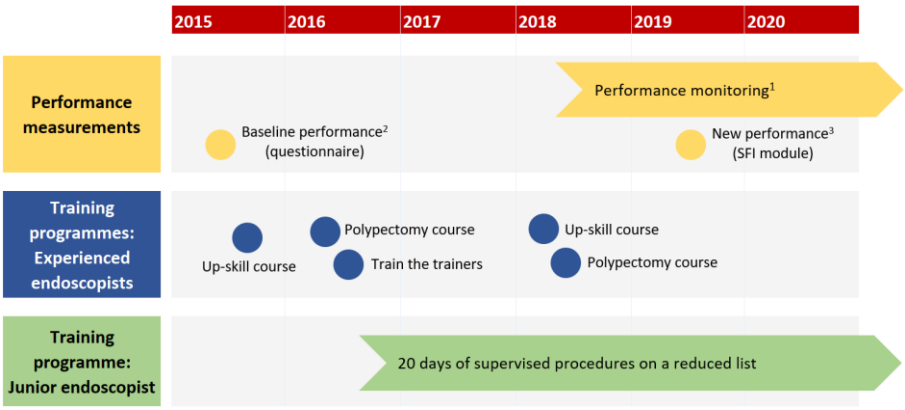

Figure 8 Timing of quality improvement initiatives

[1]Individual endoscopist performance monitoring. [2]Baseline department performance based on questionnaires. [3]New department performance based on data from the quality monitoring system

3.2.1. 2015: BASELINE PERFORMANCE (PAPER-BASED SURVEY)

The 2015 performance baseline at Aalborg University hospital was established using a single page paper-based survey. The survey included the endoscopist's identification number and educational background, indication for colonoscopy, information about cecum intubation (or reason for lack of intubation), medicine use, NRCL and number of found polyps. Initial information sessions at both Hobro and Aalborg Hospital were held to inform endoscopists and assistant nurses about the upcoming survey. The survey was distributed with assistance from the medical secretaries. Each survey was labelled with the patient CPR number and distributed together with the paper-based health records every morning to endoscopists (common procedure in 2015) for a 14-week period. Unreturned questionnaires were identified from booking records and completed using the EHR. A total of 894 surveys were distributed with 838 surveys (93.7%) returned by endoscopists. Returned surveys were digitized using EpiData Manager and EntryClient (Epidata association – comprehensive data management and basic statistical analysis system v4.6.0.2, Odense, Denmark) and subsequently exported for statistical analysis in Stata MP 15.1 (StataCorp 2017, College Station, TX, US).[98–100]

3.2.2. TRAINING PROGRAMMES FOR EXPERIENCED ENDOSCOPISTS

The colonoscopy quality improvements were based on a series of courses held by a group of English endoscopists considered leading experts in teaching colonoscopy.[101,102] A total of two skills upgrading, two polypectomy and one train-the-trainer courses were held from the autumn of 2015 to the spring of 2018. The

timeline of courses is seen in Figure 8. Each course lasted two days and had six participating delegates. Colonoscopies were live-streamed by two cameras covering the endoscopy room and the colonoscope video feed with both videos displayed in the adjoining room. The delegate performing the procedure and the expert in the endoscopy room were both issued with wireless microphones. The remaining delegates then watched and discussed the case in the adjoining room. The skills upgrading course covered areas such as scope handling, patient positioning and techniques to improve visualization and a common colonoscopy teaching language. The polypectomy course covered expert advice to improve PDR/ADR, polyp classification and polyp removal. The train-the-trainers courses were offered to selected endoscopists expected to play a future role in training junior endoscopists. The main focus was to acquire conscious competence to facilitate effective learning and skills acquisition.

3.2.3. TRAINING PROGRAMME FOR JUNIOR ENDOSCOPISTS

A module-based colonoscopy training programme was developed for junior doctors. The programme consisted of a theory and simulator course followed by 20 days of supervised colonoscopies with a reduced list of six colonoscopies per day. The training days are to be completed within 3 months. Feasibility testing was conducted by five junior endoscopists in 2015 (1st to 3rd year surgical residents). Important lessons were learned in relation to organizing and scheduling the module-based training programme. Cancelled training days and surgical pagers provided anything but an effective and calm training environment. The solution was to move all training days to the outpatient endoscopy unit at Hobro hospital. The physical distance proved an effective barrier against last-minute cancellation and removed most disturbances during training days. Since the autumn of 2016, all first-year surgical residents have been enrolled in the modular training programme. Competence improvements are tracked continuously using the Assessment of Competence in Endoscopy (ACE) by the ASGE. Four endoscopy simulator tests using the Simbionix GI mentor and the Immersion Medical AccuTouch are performed before, midway and at the end of the module-based training programme.[66,103] At present, 14 junior doctors have completed the programme. Evaluation and data analysis will take place when 15 doctors have completed the programme.

3.2.4. THE QUALITY MONITORING SYSTEM

Development of the quality monitoring system began in March 2018 in cooperation with the regional business intelligence unit (BI unit). The quality monitoring system was developed as a supplementary file (SFI). An SFI is an electronic sheet completed during every colonoscopy and saved as part of the EHR. The file collects information on colonoscopy indication, endoscopist, CIR, polyps (numbers found , removed and retrieved), WT, comfort score and patient characteristics. A full list of variables and categories obtained from the SFI is available in Supplementary table A. An initial version was uploaded to a testing environment and tested on a small scale on live endoscopies with additional adjustments of layout and mandatory input fields. The

final version was released in October 2018 and implemented as a stand-alone SFI accessible under "new procedures" and through the "standard of care" regime, a regime familiar to the assistant nurses. The assistant nurse was assigned responsibility for completing the SFI. Feasibility testing began at Hobro hospital in November 2018. Implementation was conducted at a morning teaching session explaining the need and rationale of performance monitoring using current guidelines and data obtained from the paper-based survey followed by the presence of the PhD author for two days in the endoscopy rooms for guidance and assistance related to the SFI. Implementation followed at Aalborg hospital in January 2019, Thisted endoscopy unit in February 2019, Frederikshavn endoscopy unit in May 2019 and Hjørring hospital in June 2019. Raw outputs are generated from the SFI by the BI analysis unit biannually and on special requests. Individual performance reports are sent by e-mail to each endoscopist and the head of the department. Each performance report contains individual key performance indicators compared to department average and/or recognized performance goals. Anonymized outputs are also presented at endoscopy unit meetings.

3.3. STUDY III: COLONOSCOPY ADVERSE EVENTS

Data for Study III were obtained through EHR review. The BI unit provided a list of patients in the North Denmark Region who had an outpatient colonoscopy performed from 1 January 2015 to 31 December 2018 and who matched one of the following criteria:

- Readmitted within eight days from outpatient colonoscopy
- Died within 30 days from outpatient colonoscopy
- Was assigned a colonoscopy complication code within 8 days of colonoscopy.

A list of outpatient endoscopy unit codes is available in Supplementary table B.
Colonoscopies were identified using the NOMESCO Classification of Surgical Procedure Codes KUJF32 and KUJF35, colonoscopy with and without biopsy.[95] Colonoscopy complication codes were identified from Danish ICD-10 codes and defined as: DT812G1: Perforation or lesion during colonoscopy; DT810J1: Bleeding following colonoscopy; DT810J: Bleeding following endoscopy; DT888U1: Medical complication to colonoscopy; DT888U: Other complication to colonoscopy; and DT888L: Post polypectomy syndrome.

Data capture from the EHR was conducted using the RedCap data capture tool.[104] An initial data capture tool was designed and tested on 25 patients and small adjustments were continuously made to adjust logic branches and cover all AEs in concordance with the ASGE lexicon.[72] The final RedCap data capture tool covered up to 199 variables related to each colonoscopy. At the production stage, the first and second author in Study III entered 25 cases separately and agreement was sought. Another 25 cases were entered separately with complete agreement on categorizing, attributing

and severity grading of AEs in 24 out of 25 cases (96%). Upon completion of all the 1,141 potential AEs, data were exported for further analysis in Stata.[100]

3.4. STUDY IV: OVERALL AND STANDARDIZED PERFORMANCE INDICATORS

Data used in Study IV were obtained from the quality monitoring system described in section 3.2.4. An output based on an irregular 8-month period served as basis for the data analysis. All patient-level data (except age, sex and indication) and findings (except binary data on CIR and polyps) were censored to protect patient confidentiality and to allow for publication in an open file repository.[105] Minimum acceptable standards were set as CIR of 90% similar to UK guidelines and PDR was set to 35% according to a previous study by Patel et al.[50,106] Overall CIR and overall PDR were compared to standardized CIR and standardized PDR. Standardization was made by adjusting for endoscopist, colonoscopy indication, patient sex and patient age. Comparison of overall and standardized performance markers were conducted by comparing absolute changes, rank changes and correlations using Kendall's τ.

3.5. STATISTICAL ANALYSIS

Study I: Statistical analysis was conducted using SAS 9.4 (SAS Institute, Cary, North Carolina, US). Confidence intervals (CIs) for rates were calculated assuming a Poisson distribution. Relative risks (RRs) when comparing countries were calculated according to Altman.[107] A multivariable Poisson regression model was constructed using the PROC GENMOD procedure. An interaction between hereditary CRC and patient age was found. For this reason, hereditary CRC was stratified by age (below and above 60 years of age).

Study II: Statistical analysis was conducted using Stata MP 15.1.[100] The chi-square test was used for univariable comparison. Multivariable analysis controlling for age, sex and colonoscopy indication was conducted using logistic regression. Colonoscopy performance reports were generated from raw data outputs delivered by the BI unit. A series of Stata loops generated a performance spreadsheet containing key performance indicators with 95% CI on all endoscopists. The spreadsheet was subsequently imported to a Word template using the Microsoft Word "mail merge" function to generate individual performance reports.[108]

Study III: Statistical analysis was conducted using Stata MP 15.1.[100] The incidence of AEs was calculated using exact 95% binomial CIs (Clopper-Pearson). Two-sample test of proportions was used to compare groups (prtest). CIs on continuous variables were calculated assuming normal distribution.

Study IV: Data analysis were conducted in R using the following packages: "Data.table", "riskRegression", "DescTools", "xlsx", "Publish" and "Hmisc".[92,109–114] CI on continuous variables were calculated assuming normal distribution and CIs

on binary variables were calculated using the Wilson interval.[115] Standardized CIR and standardized PDR were based on a logistic regression model adjusting for endoscopist, colonoscopy indication (screening/diagnostic), patient gender (male/female) and patient age (continuous). Standardized CIR and standardized PDR were calculated assuming every endoscopist performed a single colonoscopy on all patients in the database using the results from the logistic regression model. CIs on endoscopists performance in the standardized models were calculated using bootstraps with 1000 repetitions and Wald type CIs. Scatter plots of overall CIR vs standardized CIR and overall PDR vs standardized PDR were constructed to evaluate outliers and variability. Correlation was estimated using Kendall's τ.

3.6. ETHICAL CONSIDERATIONS

Study I: Retrospective register-based studies are not subject to ethical committee evaluation in Denmark. The study was registered with the Danish Data Protection Agency through the Capital Region (P-2019-348). All data had encrypted CPR number to protect individuals.

Study II: The paper-based survey and live-teaching colonoscopy courses were reported as a research project within the North Denmark Region (id: 2015-70). Patients participating in live-streaming courses were informed about the courses in advance and all patients gave written and oral consent. Paper-based surveys were stored in locked storage containers and digitally on locked, encrypted devices. Endoscopist name was irrevocably anonymized.

Study III was conducted as a quality assurance project under the Danish health care act § 42d. The study was approved by the heads of all participating departments according to the North Denmark Region guidelines by March 2019. Data were collected from EHR and stored confidentially within the North Denmark Region RedCap system.[104] Data exported for statistical analysis in Stata were stored on locked, encrypted devices. All patient level data such as age, sex, dates and hospital were omitted in the published paper to protect patient integrity and privacy. Previous diseases are described in broad terms and only included if necessary for the context.

Study IV was conducted on data extracted from the SFI. All data except patient age, patient sex, colonoscopy indications, endoscopist, cecum intubation or polyp detection were removed. Endoscopist name was irrevocably anonymized to allow for publication of primary data.

CHAPTER 4: RESULTS

This section gives a brief summary of the findings from each published or proposed paper.[74,93,94] Tables and figure already presented within the papers are omitted, while results not presented within the papers are presented in full.

4.1. STUDY I: DANISH PCCRC-3YR RATES AND FACTORS ASSOCIATED WITH PCCRC

4.1.1. DANISH PCCRC-3YR RATES

- The Danish PCCRC-3yr rate from 2001-2010 varied from 2.5% to 9.1% depending on the method used for calculation (Supplementary figure A)
- The Danish PCCRC-3yr rate was significantly higher than the English NHS PCCRC-3yr rate from 2001-2010 (RR 1.12 (95%CI 1.05-1.19)) using the Cooper method[58,63,74]
- The Danish PCCRC-3yr rate was significantly higher than the Swedish PCCRC-3yr rate from 2001-2010 (RR 1.15 (95%CI 1.06-1.24))[74,85]
- The Danish PCCRC-3yr has been falling gradually from 22.5% in 2001 to 7.9% in 2012 using the WEO consensus method. A large fall occurred from 2003 (21.4%) to 2004 (9.5%).[74]

4.1.2. MULTIVARIABLE REGRESSION ANALYSIS

- The multivariable regression analysis found the following factors to be significantly associated with an increased risk of PCCRC[74]
  - Year of colonoscopy
    - 2001-2006 vs 2007-2012: RR 1.55 (95%CI 1.40-1.71)
  - Charlson Comorbidity Index
    - 1 vs 0: RR 1.20 (95%CI 1.03-1.40)
    - 2 vs 0: RR 1.25 (95%CI 1.06-1.48)
  - Colon tumour site
    - Transverse vs rectum/sigmoid: RR 1.57 (95%CI 1.28-1.94)
    - Cecum/ascending/hepatic flexure vs rectum/sigmoid: RR 1.85 (95%CI 1.64-2.08)
    - Colon not otherwise specified vs rectum/sigmoid: RR 2.08 (95%CI 1.74-2.49)
  - Tumour size
    - T1/T2/Dukes A vs T3/T4/ Dukes: RR 0.70 (95%CI 0.61-0-81)
  - Ulcerative colitis
    - Yes vs no: RR 3.44 (95%CI 2.79-4.23)
  - Hereditary CRC (age<60 years old)
    - Yes vs no: RR 7.39 (95%CI 5.77-9.47)
  - Hereditary CRC (age>60 years old)

    - Yes vs no: RR 3.81 (95%CI 2.74-5.31)
- Diverticulitis
    - Yes vs no: RR 3.25 (95%CI 2.88-3.66).

4.2. STUDY II: IMPROVING COLONOSCOPY QUALITY THROUGH INDIVIDUALIZED TRAINING PROGRAMMES

4.2.1. 2015: BASELINE PERFORMANCE (PAPER-BASED SURVEY)

- A total of 838 out of 894 colonoscopy quality survey were returned by endoscopists (93.7%). Unreturned surveys were completed from EHR[94]
- The colonoscopy quality survey was validated against the EHR on 100 colonoscopies with no errors related to CIR or PDR
- CIR on returned surveys was 89.7%, while CIR on unreturned surveys was 48.2% ($p < 0.001$)
- Overall CIR was 87.1% (95%CI 84.8%-89.3%) with a lower CIR among diagnostic colonoscopies (85.5% (95%CI 82.6%-88.1%)) than among screening colonoscopies (92.2% (95% CI 87.8%-95.4%))[94]
- Overall PDR was 33.7% (95%CI 30.6%-36.9%); 26.5% (95%CI 23.2%-30.0%) for diagnostic colonoscopies and 55.9% (95%CI 49.1%-62.7%) for screening colonoscopies[94]
- Individual CIR varied from 74.1% (95%CI 64.6-83.6) to 96.3% (95%CI 92.1-100.0) and individual PDR from 20.3% (95%CI 13.1%-27.5%) to 55.8% (95%CI 40.4%-71.3%) Baseline characteristics are available in Supplementary table C
- Logistic regression adjusting for endoscopist, patient age, patient sex and colonoscopy indication found significant differences in both CIR and PDR. The worst CIR performer had an OR of 7.26 (95%CI 2.04-25.85) for not reaching the cecum (compared to the best) (Supplementary table D). The OR for finding at least one polyps was 2.92 (95%CI 1.38-6.17) when comparing the best and worst endoscopist (Supplementary table E).

4.2.2. 2019: NEW PERFORMANCE (ELECTRONIC SFI)

An output from the quality monitoring system covering a 14-week period was obtained in the spring of 2019 (1,488 colonoscopies).

- Overall CIR increased from 87.1% (95%CI 84.8%-89.3%) to 92.1% (95%CI 90.6%-93.4%) and overall PDR increased from 33.7% (95%CI 30.6%-36.9%) to 41.7% (95%CI 39.1%-44.2%) from 2015-2019[94]
- The increase in both CIR and PDR was significant in the univariable analysis ($p < 0.001$)[94]
- Multivariable logistic regression adjusting for indication, patient sex and patient age found a significantly higher OR of reaching the cecum in 2019 than in 2015, OR 1.63 (95%CI 1.24-2.15). The OR for polyp detection in 2019 was 1.13 (95%CI 0.94-1.36) compared to 2015.[94]

4.2.3. THE QUALITY MONITORING SYSTEM (AUTUMN 2019)

- The first regular 6-month output covering the entire North Denmark Region was generated in December 2019. It covered 6376 colonoscopies
- Validation of the SFI against booking records and EHR was performed at Aalborg University Hospital in the spring of 2019 covering 100 colonoscopies. Three colonoscopies were missing in the colonoscopy reporting system (SFI not completed), but cecum intubation was complete in all three cases. In five colonoscopies, the identity of the endoscopist was not reported
- Validation of data from Thisted, Hjørring and Frederikshavn is pending.

4.2.4. MAJOR COLONOSCOPY PERFORMANCE INDICATORS IN THE NORTH DENMARK REGION

- A total of 6,376 colonoscopies were performed in the autumn of 2019 by 81 endoscopist, median 50, interquartile range [19-119]
- A total of 41 endoscopists performed <50 colonoscopies during the 6-month period. They performed a total of 822 (12.9%) colonoscopies
- Major key performance indicators are found in Table 4 below:

Table 4 Key colonoscopy performance indicators in the North Denmark Region with individual endoscopist performance range compared to UK targets

	North Denmark Region		Performance range of endoscopists[1]	UK quality standards[2]
	Mean	95% CI	[min-max]	Min./aspirational
Overall CIR	92.2%	(91.5%-92.9%)	[84.3%-97.0%]	≥90% / ≥95%
Screening CIR	94.0%	(93.0%-94.9%)	[85.2%-100%]	≥90% / ≥95%
Diagnostic CIR	91.2%	(90.3%-92.1%)	[83.6%-96.2%]	≥90% / ≥95%
Overall PDR	42.4%	(41.1%-43.6%)	[9.7%-66.1%]	
Screening PDR	58.9%	(56.9%-61.0%)	[45.6%-74.6%]	
Diagnostic PDR	33.0%	(31.5%-34.4%)	[9.7%-59.7%]	
NRCL ≤ 3	88.5%	(87.7%-89.3%)	[71.8%-94.4%]	≥90%
Polyp retrieval rate	90.8%	(90.1%-91.5%)	[74.1%-99.1%]	≥90%
WT (min)	10.7	(10.5-10.9)	[5.0-20.4]	≥6 / ≥10

NRCL: Nurse-reported comfort levels. WT (min): Withdrawal time measured in minutes. CIR: Cecum intubation rate. PDR: Polyp detection rate. [1]Endoscopists with >50 observations for calculations. [2]Minimal/aspirational targets according to the UK standard. No PDR target for screening colonoscopies exists (Rees CJ et al 2016).

4.3. STUDY III: COLONOSCOPY ADVERSE EVENTS

4.3.1. OVERALL RESULTS

- A total of 49,445 colonoscopies were performed in the North Denmark Region
- A total of 1,141 colonoscopies were potentially associated with AEs and investigated in EHRs (23.07‰)
- EHR review left 489 AEs attributed to colonoscopy. The overall AE rate was 9.9‰ (95%CI 9.0‰-10.8‰)[93]
- Fatal AE rate was: 0.2‰ (95%CI 0.1‰-0.4‰); severe AE rate: 1.3‰ (95%CI 1.0‰-1.7‰); moderate AE rate: 2.5‰ (95%CI 2.0‰-3.0‰); and mild AE rate 5.9‰ (95%CI 5.3‰-6.6‰)[93]
- AEs were categorized as cardiovascular (0.65‰), pulmonary (0.36‰), thromboembolic (0.10‰), instrumental incl. perforations (0.99‰), bleeding (3.07‰), infection (0.87‰), drug reactions (0.04‰), pain (2.00‰), integument (damage to skin/bones) (0.34‰) and other (1.62‰)[93]
- Nine out of ten fatal AEs were not directly related to the colonoscopy procedure (bleeding or perforations), but caused by cardiovascular, thromboembolic or other AEs. [93]

4.3.2. COMPARISON WITH UK QUALITY ASSURANCE GUIDELINES

Colonoscopy perforations rates compared to UK quality assurance standards are found in Table 5 below. [50]

Table 5 North Denmark Region complications rates compared to UK quality assurance standards

	North Denmark Region	UK Minimal standard	UK Aspirational target
Overall colonoscopic perforation rate	1 in 1030	< 1 in 1000	< 1 in 3000
Non-polypectomy colonoscopic perforation rate[1]	1 in 2524	< 1 in 2000	< 1 in 4000
Colonoscopic perforation rate where polypectomy performed	1 in 470	< 1 in 500	< 1 in 1500
Post-polypectomy bleeding rate (moderate severity or worse)	1 in 277	< 1 in 200	< 1 in 1000
Colonoscopic perforation rate where dilatation performed	1 in 30	< 1 in 33	<1 in 100

[1]Including colonoscopies with biopsies. Minimal standard / aspirational targets according to UK quality assurance standards (Rees CJ et al 2016).

4.4. STUDY IV: OVERALL AND STANDARDIZED PERFORMANCE INDICATORS

4.4.1. OVERALL AND STANDARDIZED CIR

- Patient age (OR 0.98 (95%CI 0.97-0.99)) (per year) and screening colonoscopies (OR 1.62 (95%CI 1.31-2.01)) were significantly associated with reaching the cecum
- The maximum rank change for an endoscopist comparing overall CIR and standardized CIR was 8 positions, interquartile range [1-3]. The maximum change in CIR was 1.95 percentage points, interquartile range [0.27-0.86] percentage points. Correlation measured by Kendall's τ was 0.89 (p <0.001)
- One endoscopist, who was significantly "inferior" using overall CIR, came within 95% CI range of the 90% CIR goal using standardized CIR.

4.4.2. OVERALL AND STANDARDIZED PDR

- Patient age (OR 1.03 (95%CI 1.02-1.03)) (per year), screening colonoscopies (OR 2.97 (95%CI 2.66-3.32)) and male gender (OR 1.66 (95%CI 1.50-1.83)) were associated with polyp detection
- The maximum rank change for an endoscopist comparing overall PDR vs standardized PDR was 17 positions, interquartile range [1.5-8.5]. The maximum change in PDR was 11.21 percentage points, interquartile range [2.05-6.70] percentage points. Correlation measured by Kendall's τ was 0.69 (p <0.001)
- Two endoscopists, who were significantly inferior using overall PDR, came within 95% CI range of the 35% goal using standardized PDR. One endoscopist dropped to significantly inferior using standardized PDR.

CHAPTER 5: DISCUSSION

5.1. MAIN FINDINGS

We demonstrated that it is possible to compare PCCRC rates among countries. From a Danish perspective, it is concerning that the PCCRC-3yr rate is higher in Denmark than in both Sweden and the English NHS. However, the PCCRC-3yr rate seems to be falling over time, indicating continuing improvement in colonoscopy quality. We were able to identify individuals with a high risk of PCCRC, namely patients with a high comorbidity index, tumours in the right side of the colon, hereditary CRC, ulcerative colitis and diverticulitis. If utilized properly, this knowledge may help reduce PCCRC-3yr rates.

Our study to improve colonoscopy quality was successful in improving the CIR, although the results on the PDR were mixed. We successfully established a colonoscopy quality monitoring system. The CIR and PRR are significantly above the minimum quality assurance threshold set in the UK, and WT is above the UK aspirational target. There are large inter-endoscopist differences in performance, and many endoscopists perform relatively few procedures. A module-based training programme for junior doctors has now been successfully implemented.

Colonoscopy AEs remains an important issue as AEs occur in around 1:100 colonoscopies. The rates of perforations and bleedings in the North Denmark Region are just below or above the minimal UK quality assurance standards depending on which exact measurement is used. The study revealed AEs extending beyond directly procedure-related complications. Nine out of ten fatal AEs were caused by non-procedure-related AEs.

Standardized performance markers are useful for direct comparison of endoscopists performance. Standardization had little effect on the CIR and a more pronounced effect on the PDR. Overall CIR is a reasonable performance indicator but care should be taken when interpreting data on potential inferior performers. Overall PDR becomes unreliable in situations where an endoscopist has an outlier case-mix.

The following sections discuss the results of each study with a focus on the methods used and their limitations in a general perspective. The section supplements the four papers.

5.2. STUDY I: DANISH PCCRC-3YR RATES AND FACTORS ASSOCIATED WITH PCCRC

A common PCCRC methodology

Re-calculating PCCRC-3yr rates for direct comparison when new studies emerge using their own unique method is impractical, but unfortunately necessary. As seen from Supplementary figure A, the Danish PCCRC-3yr rates vary from 2.5% to 9.1% depending on the method used for calculation.[4,6,8,58] Selecting a methodology for future reference requires careful consideration of advantages and drawback related to each method. The *le Clercq* and the *Bressler* methods had designs that might limit their use as a common method. The *le Clercq* method simply used PCCRC divided by all CRCs diagnosed in the population whether or not they were diagnosed by colonoscopy. The result is a large denominator and a small PCCRC rate. It is simple, but does not account for the general use of colonoscopy within a population. If few colonoscopies are performed, the rate will be negligible. *Bressler* chose a rather restricted definition of PCCRC as individuals were also required to *not* have a colonoscopy less than 6 month from diagnosis. This effectively excluded any PCCRC that was subsequently diagnosed by colonoscopy, leading to a smaller numerator. The methods proposed by *Cooper* and *Singh* were almost similar, except that the *Singh* method allowed for a CRC to be counted in both the PCCRC and DC group. Morris et al. developed their "new colonoscopy method" (a fifth method) on the basis of this comparison.[63] The approach was very similar to that of the *Singh* methods but changed the analysis from year of CRC to year of colonoscopy, thus making it easier to track performance improvement over time.[63]

The WEO consensus method published in 2019 closely follows the method by Morris et al., but it allows multiple CRCs in each individual.[64] For instance, two CRC occurring years apart can, in principle, cause two DC colonoscopies and two PCCRC colonoscopies in the same individual. Only the last colonoscopy in each DC or PCCRC interval is counted. If an individual has two colonoscopies, e.g. 12 months and 11 months before a CRC, only the colonoscopy 11 months before the CRC is counted in the PCCRC category. This might seem as a smart choice as the PCCRC-3yr rate is used as an epidemiological tool with little information available for each procedure as the first colonoscopy might simply be repeated due to a bad bowel preparation. However, this application also has drawbacks. We have experienced cases with multiple colonoscopies in the PCCRC category (up to three) that all missed the same CRC. They will be counted only once by using the WEO consensus method. Similarly, the DC interval of 6 month can be problematic. If a symptomatic patient undergoes a colonoscopy initially missing the CRC, this individual is likely to undergo further examination shortly after. A common examination would be CT. The sensitivity of CT to detect CRC depends on tumour size, but is reported at 70%-100%.[116,117] If a CRC is suspected, a new colonoscopy is likely performed within 6 months, and the initial colonoscopy will not be counted as a PCCRC colonoscopy. For this reason, others have used a shorter DC interval of 3 months.[118] However, the WEO methods are set to be universally applied to different countries and jurisdiction

over a long period of time, making the 6-month interval a safer choice to ensure that a slow diagnostic process does not lead to misclassification. The use of year of colonoscopy rather than year of cancer does provide better tracking of colonoscopy quality over time as mentioned earlier, but it also has the unwanted effect that reported numbers will be somewhat old. Thus, 3 years of follow-up, another 1 or 2 years to ensure that all databases are updated and to process various applications followed by 1 year of data management and publication means that published rates are likely to be 6 years old.

Two other factors related to calculating PCCRC rates should also be noted: The relative sensitivity of the date of CRC diagnosis and the effect of change in the use of colonoscopy over time. From 2001-2010, less than one third of CRCs had a colonoscopy within the preceding 3 years (Denmark: 29.4%; the English NHS: 31.7%)[63,74] (Supplementary figure A). Sigmoidoscopy was likely more common in this period, partly explaining the low numbers, but the exact diagnosis date might also be important. When an individual is admitted due to various CRC-related symptoms and a CRC is confirmed a few days later (by colonoscopy), the exact diagnosis date will be of utmost importance in PCCRC-3yr rate calculation. If the diagnosis date is coded as the date of admission, the CRC will not become a DC but simply be omitted from calculations. If the CRC diagnosis date is coded as the later date corresponding to the date of pathology verification or the date of colonoscopy, it will be counted as a DC. Attention to coding algorithms is needed to ensure that rates are comparable.

Our finding of falling PCCRC-3yr over time is comforting, but if the way colonoscopy is used changes over time, the PCCRC-3yr rate might fall without any real quality improvements. Today, preoperative histological CRC confirmation is almost always performed, but the situation was likely different 20 years ago. Such a phenomenon seems to have affected the Danish numbers, especially in the period from 2003 to 2004 as the PCCRC-3yr rate fell from 21.4% to 9.5%.[74] This fall is mainly caused by an almost 3-fold increase in DC, while PCCRC remains relatively constant (Paper I: Table 3).[74] As seen from Supplementary figure B, the driving force behind the increase in DC colonoscopies is "colonoscopies with biopsies", indicating a preoperative regime shift.[74]

The use of national registries

Calculating the PCCRC-3yr rate requires reliable registries in relation to both procedures and CRCs. A previous study from the US found that almost half of PCCRCs were due to registry errors.[119] The Danish registries are generally known to be accurate with a high data quality, but procedures and cancers can be miscoded, misclassified or misdated.[43,82] A previous Danish study investigated PCCRCs in another context and reviewed 101 PCCRC cases identified from the DNPR/DCR.[118] The timeframe for DC was just 0-3 months with an increased risk that some CRCs would incorrectly be assigned to the PCCRC group. Nonetheless, 89% of PCCRCs were correctly assigned. Several other procedure codes have been validated in the

DNPR. Procedures such as hip replacements, appendectomy and cholecystectomy have been shown to have a positive predictive value (PPV) of 99-100% against journal records.[82,120] Validating CRC against journal records is less simple as diagnostic criteria for CRC might change over time. In the DNPR, a cancer diagnosis is coded as a simple ICD-10 diagnosis, while the DCR relies on complex information obtained from the DNPR, separate registrations and pathology.[43] CRC has been validated in the DCR against patients registered in both the DNPR and the DCR at a PPV of 88.9%.[121] The cause of the lower PPV was missing registrations in the DCR, e.g. on patients > 75 year of age and CRC with unknown location.[121] These findings indicate less complete registration of severely ill and older patients in the DCR. Since our study used CRC diagnosis from the DCR, there is a risk that some older patients and patients with unknown tumour location have been missed in our analysis.

A review on validation of non-cancer diseases in the DNPR from 2015 by Schmidt et al. gives a good oversight of the PPV and sensitivity of using the DNPR for diagnostic purposes.[82] In general, studies report good PPVs and sensitivities, but using the DNPR is not entirely unproblematic. Relevant to our study, Crohn's disease and ulcerative colitis have been validated with a PPV of 97.2% and 90.3%, respectively, but the identified studies are almost 25 years old and did not include outpatient visits.[122] More recently, in 2010, diverticular disease was validated, showing a PPV of 98.0%.[123] Newer incidence studies on IBD based on the DNPR have applied a criterion according to which a specific number of positive records was required before a positive diagnosis was assigned.[124] Such criteria would likely select individuals with more severe disease. Our use of a single previous record of either Crohn's disease or ulcerative colitis could underestimate the risk of PCCRC as it might include a large proportion of patients with mild disease. Our definition of "hereditary CRC" as a pool of ICD-10 diagnosis codes should be considered when interpreting the results. Diagnostic criteria for hereditary CRC have changed over time, and we strongly suspect that the ICD-10 coding was inconsistent in relation to which hereditary code was used. The result is likely to be a heterogeneous group of hereditary CRC patients with Lynch syndrome, hereditary nonpolyposis CRC, different polyposis syndromes and individuals with an increased familial risk. Each subgroup has a highly different risk of CRC.[125,126] Adding supplementary data from the Danish Hereditary Non-Polyposis Colorectal Cancer Register would be beneficial if the relationship between PCCRC and hereditary CRC were to be explored further.[127] However, attention to PCCRC rate calculations is warranted in individuals where intensive surveillance is performed. The Danish recommendation for Lynch syndrome is biennial colonoscopy. Any individual with Lynch disease diagnosed with CRC while adhering to the control programme would be registered with both a DC and a PCCRC. If all individual with Lynch disease adhered to the biennial colonoscopy recommendation, this would inflate the PCCRC-3yr rate to 50%. A similar effect could overestimate the risk of PCCRC in patients with ulcerative colitis, but Danish guidelines do not recommend intensive surveillance, albeit additional colonoscopies for diagnostic purposes are likely.[128]

5.3. STUDY II: IMPROVING COLONOSCOPY QUALITY THROUGH INDIVIDUALIZED TRAINING PROGRAMMES

Reporting bias

Setting up a colonoscopy quality monitoring system requires careful consideration to avoid reporting bias, a problem easily perceived from the 2015 baseline survey. The response was good with 93.7% of the surveys being returned by endoscopists with an overall CIR of 89.7%, very close to the minimal acceptable standard. Unfortunately, further data analysis and validation revealed that the CIR for non-responders was just 48.2%, causing the overall CIR to decline to 87.1%, which is significantly below the 90% minimal standards.[49] To our knowledge, reporting bias on CIR has not been directly evaluated in any large-scale setting; however. registration bias is known to occur in other colonoscopy quality databases such as the Norwegian Gastronet database.[129] It is impressive by size, but relies on positive reporting. A total of 12 out of 20 hospitals investigated had < 90% of procedures recorded in the Gastronet Database compared to the Norwegian National Patient Register. A direct comparison between reported and non-reported procedures has not been made, but longer procedure times and a low AE rate have been associated with incomplete registration in the database.[129] A similar issue could also have affected the UK quality audit from 2013, but nurses (not endoscopists) were charged with gathering data and validation was performed without indication of selection bias.[3] The overall risk of selection bias is a "feel good" database with impressive performance, but it might not mirror the actual quality. A solution to counter reporting bias is to deploy a standardized reporting system within the EHR that automatically reports to quality databases. The English National Endoscopy Database is based on such a system with automatization of the data capture process; however, histopathology is currently not included.[77] The Danish CRC screening programme is based on a series of codes related to each procedure, thus also relying on positive reporting. The actual coding is conducted by medical secretaries based upon information from the endoscopy reports, which probably limits reporting bias. Validity has been shown to be good, but with some incomplete coding related to specific codes.[130] Interpretation of databases (especially the affected codes) should be undertaken with caution; however, they are more likely incomplete than affected by bias.

Implementing the reporting system

Upon introducing the system, some concerns were raised by both assistant nurses and endoscopists. Some endoscopists worried how data were going to be used and questioned whether the system was needed; assistant nurses had concerns about time spent filling in the SFI and they were a bit puzzled why they, not the endoscopists, had to complete the form. The 2015 baseline survey became a useful tool. Results from the survey were presented on both local and national meetings explaining "reporting bias", the low overall CIR and the large individual performance differences (performance gaps). The identification of known "performance gaps" in combination with guideline recommendations on performance monitoring helped provide a smoother implementation process.[49,131] The SFI was designed to be completed in less

than 2 minutes once users had familiarized themselves with the concept. This might seem negligible, but regulatory creep could become a problem. An editorial in Gastrointestinal Endoscopy by an endoscopist describes how he spends 20 minutes filling in seven forms after every colonoscopy. The endoscopy nurse fills in another five forms.[132] It is doubtful whether such rigid documentation is beneficial for the quality of the colonoscopy.

Assigning assistant nurses responsibility for completing the SFI was successful in reducing reporting bias. As mentioned in section 4.2.2, validation was performed at Aalborg University Hospital on 100 colonoscopies without indication of reporting bias. It did, however, reveal that some SFI were completed without endoscopist id. Unfortunately, a mandatory "endoscopist id" input field (with access to a database of endoscopists) cannot be programmed in the current EHR.

Assigning responsibility for completing the SFI to the assistant nurse gave rise to some unforeseen problems at the North Denmark Regional Hospital. Endoscopy units under their jurisdiction provide sedation by a nurse anaesthetist unfamiliar with the use of EHR and with little experience related to endoscopic procedures. We suspect the use of nurse anaesthetists could lead to a higher proportion of incomplete or missing SFIs. Validation of SFI data from the North Denmark Regional Hospital is pending.

The risk of gaming

The introduced quality monitoring system relies on PDR, not ADR. The absence of incorporation with histopathology could result in unwanted behavioural change on the part of the endoscopists, commonly referred to as "gaming the system", by removal of non-adenomatous lesions. Several studies have investigated the PDR/polypectomy rate against the ADR and found them to be a good marker of the ADR.[54,106,133] Munchie et al. evaluated the effect of the PDR/ADR ratio when introducing performance monitoring based on PDR alone and found no indication of gaming.[54] UK quality assurance standards accept the PDR as a surrogate marker if the PDR/ADR ratio has been validated.[50] US studies (that found PDR to be a good marker of ADR) have found PDR/ADR conversion rates of 0.64-0.68.[54,55,133] Conversion rates in a Danish context do seem to be higher, at least in the screening context. Comparing our 2015 PDR (from the baseline survey) with ADR reported in 2015 (from the Danish screening programme), we found almost identical PDR and ADR (55.9% and 54%, respectively). A PhD study from the Central Denmark Region validated PDR against ADR on a cohort of 8,256 screening colonoscopies. PDR from the SFI was 51.9%, while ADR was 50.9%.[79] The close relationship between PDR and ADR leaves very little room for PDR/ADR gaming. It should be noted that the risk of gaming extends beyond the PDR/ADR issue. One-and-done gaming refers to endoscopists removing a single adenoma with little care for examining the remaining colon. One-and-done gaming has been documented in a study from the US where a veteran affairs hospital was comparted with private practices.[134] ADR was comparable, but the number of

total adenomas found was higher at the veteran affairs hospital. One-and-done gaming might be exacerbated by economic incentives where removal of one adenoma (but not additional ones) provides higher reimbursement. One-and-done gaming can be countered by measuring total adenomas or mPPP/mAPP (see section 1.7) to provide a better measurement of the overall ability to find polyps.[135] MPPP are not completely resistant to gaming, but it would require a dedicated effort to remove multiple non-adenomatous lesions to boost mPPP. "Indication" gaming has also been described.[90] The focus on PDR/ADR is often more pronounced on screening colonoscopies than on other indications. If a monitoring system allows for changing indication, an endoscopist might boost his/her numbers on a screening colonoscopy by assigning the screening indication whenever an adenoma is found. Currently, the only option to identify indication gaming is manual validation. Since the SFI is completed by the assistant nurse, indication gaming would require close cooperation between the assistant nurse and the endoscopist to occur. Indication gaming in relation to reports generated by the Danish CRC screening programme is not possible as screening patients are identified and invited from a central registry.

The effect of quality monitoring

An endoscopist quality monitoring system has the ability to detect underperformers, but it might also by itself introduce behavioural change. This effect is generally known as the Hawthorne effect, where participants change behaviour in response to their awareness of being observed.[136] The effect is believed to be higher when combined with an effective feedback mechanism. An audit and feedback system in colonoscopy has shown to improve PDR/ADR by 10-20% in some studies.[131] Tinmouth et al. refer to two types of social norms that might enhance the effect of feedback: *prescriptive social norms* and *descriptive social norms.*[131] *Prescriptive social norms* refer to each individual aligning his/her behaviour with behaviour expected from a recognized authority; in our case by comparing individual performance using performance goals from recognized societies (e.g. the Danish Colorectal Cancer Screening programme, ESGE guidelines).[34,52] *Descriptive social norms* refer to aligning behaviour with the rest of the group. Providing performance goals such as department average allows the endoscopist to see whether he/she is performing similarly to the rest of his/her peers. Both concepts were utilized in our feedback report (available in Paper II). Another important subject is timely feedback. We chose to provide feedback twice annually, which is less than the quarterly feedback often used in other studies.[137,138] This choice is, however, a trade-off between giving timely feedback and achieving a sufficient number of procedures. Since half of our endoscopists performed < 50 colonoscopies per 6 months, providing feedback more frequently would result in numbers being too small for any meaningful feedback.[139,140] A discussion of the number of procedures required for meaningful feedback follows in section 5.5.

5.4. STUDY III: COLONOSCOPY ADVERSE EVENTS

Identifying adverse events

Setting up a reliable reporting system for colonoscopy AEs can be complex depending on the setting and jurisdiction.[141] The Danish CRC screening programme documented that AEs occur three times more often than reported from complication codes alone.[88] A validation study of the Danish Colorectal Cancer Screening database found a high agreement between the database and hospital records, but newly introduced codes (thus relatively unfamiliar to the medical staff) had a lower validity.[130] AEs occurring before the patient is discharged can, in principle, easily be recorded as part of the EHR or by a list of complications codes as described in section 3.3.[142] However, even for an experienced staff, an AE occurring on the same day as the procedure will be rare. Relative unfamiliarity with the registration codes combined with a potentially stressful environment during the AE could leave AEs undocumented. The problem related to the unfamiliarity of registration codes is likely exacerbated when AEs occur after discharge from the endoscopy unit. Individuals are commonly readmitted at emergency departments with little knowledge of colonoscopy complication-related coding. It is questionable whether AEs identified from positive reporting alone will be reliable.

The method described in section 3.3 to identify AEs is not identical to the methods described in Paper III, as complication codes were omitted in the submitted paper.[93] Of the 489 AEs, 19 had a documented colonoscopy complication code. A total of 16 patients with AEs identified from complication codes were readmitted for at least one night. Three patients with AEs identified from complications codes were observed without being admitted overnight, but all three patients were moved from the endoscopy unit to another department for better monitoring and thus identified as readmitted. The use of complications codes did not identify any additional AEs.

European and ESGE guidelines recommend using 30-day mortality review besides readmission rates. However, in our study, few additional AEs were identified based on this recommendation.[49,73] Of the 489 patients in whom AEs were identified, 18 died within 30 days of the procedure. A total of 16 individuals were readmitted within 8 days and thus identified anyway. Eight of the 16 individuals had a non-fatal AE, but died of unrelated causes within 30 days of colonoscopy. The two additional patients with fatal AEs identified from the 30-day mortality criteria were both attributed as "*possible*". The two fatal cases of AEs occurred more than 8 days after colonoscopy and were caused by changes in anticoagulants therapy and atrial fibrillation in relation to colonoscopy.

Sole reliance on readmissions to identify AEs has two major drawbacks: Mild AEs might be missed; and in some countries like the US hospitals and endoscopy units commonly operate under different jurisdictions. Without a common EHR system reliance on readmissions are likely to make AE reporting unreliable.[72] A French study classified their AEs in the same way as us, using the ASGE lexicon.[143] AEs were

identified through surveys to patients and general practitioners with telephone follow-up and review of medical records. Overall, the AE rate was higher in the French study than in our study, but only due to their finding of additional mild AEs (Paper III). In general, the inability to identify AEs from readmissions has led to various other methods being used, e.g. voluntary reporting, telephone interview or postal surveys.[72,87,144] Unfortunately, the use of different methodologies makes comparison of AE rates difficult.

The timeframe for investigating adverse events

The timeframe for identifying AEs in relation to colonoscopy is debated and ranges from 3 to 30 days depending on study and guidelines used[49,50,71,72,87] The ESGE and European guidelines recommend a 7-or-8-day follow-up, the ASGE a 14-day follow-up, while a 30-day follow-up in relation to bleeding and perforations is recommended in the UK.[49,50,52,72] Previous studies have investigated the timeframe within which perforations and bleedings occur after colonoscopy. Case stories of late perforations diagnosed weeks after colonoscopy have been described, but a review by Panteris et al. in 2009 (9 studies, a total of 236 perforations) found that 98.7% of perforations were diagnosed within 96 hours from colonoscopy.[145–147] This corresponds well with our findings that the last of our 48 patients with perforations was admitted on day 5 (Paper III). Bleedings after colonoscopy (usually caused by polypectomy) are known to occur later; thus, case stories of post-polypectomy bleedings up to day 29 have been report.[148] However, bleedings occurring that late are rare. A Chinese study covering 101 post-polypectomy bleeding cases with a 20-day follow-up found the last bleeding to occur on day 16, with 91% of bleedings occurring day 8 or earlier.[149] A US study covering 37 bleedings with a 15-day follow-up found the last one on day 14, with 86% of post-polypectomy bleeding occurring day 8 or earlier.[150] Another US study used a 30-day follow-up and found the last bleed to occur on day 13.[151] In our study, the highest frequency of bleedings was on the same day or the day after colonoscopy with daily readmissions due to bleeding continuing on a constant rate until day 8 (Study III, Figure 1). The use of an 8-day readmission rate is likely to have missed some late post-polypectomy bleedings and warrants study of whether an extended 14-day readmission period would be applicable. The use of a 30-day period as recommended by UK guidelines seems somewhat excessive from an effort-reward-ratio perspective with very few bleedings occurring in the last 2 weeks.

The rate of adverse events in the North Denmark Region

The minimum standard set by the ESGE guideline is a 7-day overall or 30-day colonoscopy-specific readmission rate of 0.5%. Our finding of an 8-day colonoscopy-specific readmission rate of 1% (95%CI 0.9-1.1%) seems high in comparison. The 0.5% recommendation is based on previous studies with different methodologies for identifying, attributing and grading AEs. Levin et al. identified 183 possible AEs from 16,318 colonoscopies by searching for specific ICD codes 30 days after colonoscopy. The EHR review left 82 “serious” complication corresponding to an AE rate of 0.5%.[152] More similar to our study was Sarkar et al., who studied 6-day emergency

readmission rates based on readmission for any cause. Overall readmission was 0.4% for diagnostic and 0.6% for therapeutic lower endoscopy, but the study also included sigmoidoscopies.[153] The previously mentioned French study used a combination of questionnaires and review of EHR to identify AEs.[143] The overall AE rate was high (2.4%). The French study used the ASGE lexicon, similar to our study. Comparing the rate of moderate and worse AEs left us with more comparable results with 4.7‰ (95%CI 3.4-6.0) comparable to our rate of 4.0‰ (95%CI 3.4-4.6). A comparison of bleedings and perforations to UK quality assurance guidelines found the North Denmark Region complication rates to be just above or below the minimal acceptable standards (section 4.3.2).[50] This still leaves room for improvement; however, the results are better than readmission rates compared to ESGE guidelines would suggest.

Non-procedure-related adverse events

The ASGE lexicon uses *unlikely, possible, probable* or *definite* to attribute each AE to colonoscopy. Attributing perforations is relatively easy due to a perfect timing after colonoscopy and because there are few other competing risks for lower-GI perforation. Bleedings are slightly more complex as lower-GI bleeding following colonoscopy might be caused by the procedure itself or be the indication for the colonoscopy. As seen from Paper III (Table 2), the majority of bleeding AEs are still attributed as "definite". However, "cardiovascular", "pulmonary" and "other" AEs are far more challenging. The ASGE lexicon does not provide detailed description of the exact use of the four attribution categories; however, a similar four-point scale is used by the WHO Uppsala Monitoring Centre to attribute drug reactions. The concept is based on four categories related to timing, absence of competing causes, response to drug removal (dechallenge) and readministration (rechallenge).[154] Only timing and absence of competing causes are generally useful in relation to colonoscopy. As described in Paper III, the majority of cardiovascular and pulmonary AEs occurred in individuals with pre-existing conditions, adding to the complexity and, unfortunately, subjectivity in attributing AEs.

In general, there are few published studies on non-procedure-related AEs. A US study found a higher OR of cardiac arrhythmia within 30 days in patients undergoing colonoscopy than in a matched cohort undergoing arthroscopy (1.21 (95%CI 1.14-1.28)).[71] A study by Warren et al. found that colonoscopy with polypectomy increased the RR of a cardiovascular event compared to a matched group that did not undergo the procedure (1.49 (95%CI 1.27-1.74)).[155] The same study also found that individuals with pre-existing comorbid conditions (diabetes, stroke, chronic heart failure, chronic obstructive pulmonary disease or atrial fibrillation) had in increased risk for AEs compared to individuals without the comorbid conditions when undergoing colonoscopy. The exact cause is unknown, but it is likely related to bowel preparation, sedation or the procedure itself. Dehydration and electrolyte disturbances can occur from bowel preparation and will likely carry a higher risk among older and frail individuals.[156,157] Dehydration and electrolyte disturbances might also lead to arrhythmias among predisposed individuals.[158] A study found that arrhythmias and

ischaemic ECG changes occurred in one third of patients with stable heart disease when undergoing colonoscopy.[159] A change in current practice might also put some individuals at an increased risk. A decade ago, older individuals were often admitted to hospital for bowel cleansing to ensure adequate hydration, but this practice has now been abandoned and bowel preparation is performed at home, occasionally with help from home care assistance. As the use of colonoscopy increases, more frail individuals are likely to undergo the procedure; and for some, a combination of bowel preparation, sedation and/or the procedure itself might by enough for an AE to occur.

5.5. STUDY IV: OVERALL AND STANDARDIZED PERFORMANCE INDICATORS

The number of procedures needed to establish inferior performance

In order to obtain a reliable estimate of endoscopists' CIR and PDR, a certain number of procedures is needed. A low number of procedures available for calculation results in wide 95% CIs and difficulty in identifying inferior performers. A study estimated that around 500 procedures are needed to establish reliable performance markers with narrow CIs.[140] The amount of procedures needed to establish inferior performance might be lower as the number of procedures required depends on the deviance from performance targets.[139] A theoretical example is illustrated below in Figure 9. The left side displays an endoscopist with a "true" CIR of 85% with 95% CI. The upper 95% CI boundary (of the 85% CIR) crosses a minimum acceptable CIR of 90% at 180 procedures. A numerical "5%" performance difference does not necessarily correspond to a specific number of procedures due to the asymmetrical CIs close to 100%. A PDR of 30% requires almost 370 procedures to become statistically inferior to a 35% minimum acceptable standard (Figure 9, right).

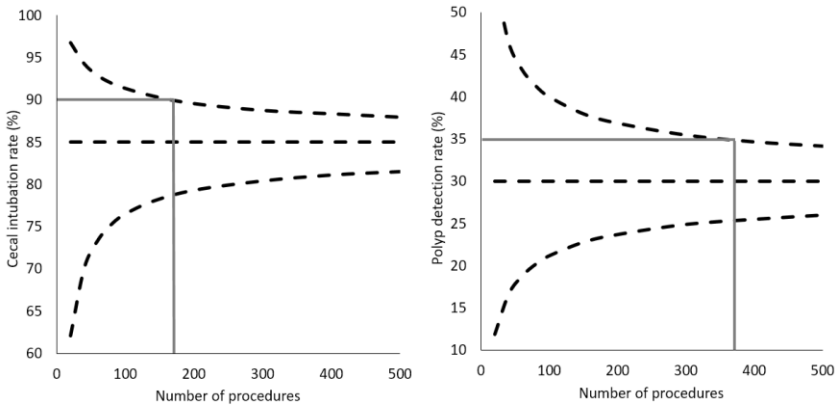

Figure 9 Procedures needed to establish significantly inferior performance

Left: A "true" CIR of 85% (with 95% CI) against a 90% CIR minimum acceptable standard. *Right:* A "true" PDR of 30% (with 95% CI) against a 35% PDR minimum acceptable standard. CIs calculated as "exact".

The concept of numbers needed to establish significantly inferior performance can also be visualized as a sharply rising curve as the "true" CIR approaches the 90% minimum acceptable performance (Figure 10). Very poor performers (a "true" CIR of 80%) requires just 40 procedures to be significantly inferior to the 90% minimal acceptable standard, but a "true" CIR of 88% requires almost 1000 procedures to establish significantly inferior performance against the minimal 90% acceptable standard.

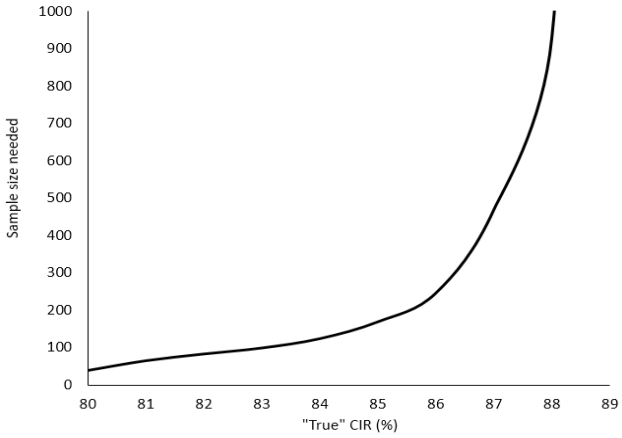

Figure 10 Sample size as a function of "true" CIR

The curve illustrates the number of procedures required to establish significantly (95% CI) inferior performance against a 90% minimum acceptable CIR.

Interpreting Figure 9 and Figure 10 in relation to data obtained from the SFI reveals limitations in our monitoring system. The median number of colonoscopies performed per endoscopist during the autumn of 2019 was just 50 procedures (interquartile range [19-119]) (section 4.2.4). From the low number of procedures follows that only severe underperforming will be statistically significant. It also highlight the problems related to splitting performance measurements into subgroups as recommended by some guidelines as this will reduce the procedures available for calculation.[9,90]

The reliability of overall CIR and overall PDR

Factors such as colonoscopy indication, patient age and patient sex can affect the CIR or PDR/ADR.[10,11,89] However, the results might be driven by large sample sizes that allows detection of even slight differences with statistical significance but with little clinical relevance. On the other hand, if the effect of a given variable is large and the proportion of colonoscopies with the variable varies between endoscopists, there is a risk that some endoscopists might be unfairly suspected of inferior performance by using overall CIR or overall PDR.

Scatterplots of standardized CIR vs overall CIR and standardized PDR vs overall PDR are available in Paper IV (Figure 1 and Figure 2, respectively). Overall CIR and standardized CIR correlate linearly and with less variability than the scatterplot of overall PDR vs standardized PDR. The maximum change in CIR rate from standardizing was just 1.95 percentage points, interquartile range [0.27-0.86] percentage points, lower than for the PDR analysis where maximum change was 11.21 percentage points, interquartile range [2.05-6.70] percentage point.

From a clinical perspective, changes occurring around the minimum acceptable PDR of 35% are most interesting as they identify potential underperformers. Rex et al. studied the effect of measuring an "overall ADR" vs "screening ADR" on changes around the minimum acceptable standard and found overall ADR to be a good performance marker.[90] In our study, four endoscopists were significantly inferior performers according to overall PDR; two of them were still inferior despite adjusting for case-mix. Some endoscopists had a rather high effect from standardization. Endoscopist 20 changed his/her overall PDR from 27.2% (95%CI 20.7%-34.7%) to 35.5% (95%CI 27.5%-43.6%) after adjusting for case-mix. The reason for the increase in endoscopist 20's performance is an unusual case-mix with very few screening procedures (1.3%) (Paper IV: Table 1). Since screening colonoscopies had an OR of 2.97 (95%CI 2.66-3.32) for finding polyps (compared to diagnostic colonoscopies), it becomes more challenging for endoscopist 20 to reach the minimum acceptable PDR of 35%. The use of overall PDR can result in some endoscopists being unfairly suspected of inferior performance.

Few studies have investigated overall CIR vs screening CIR, but a Norwegian study found similar CIR among different colonoscopy indications, concluding that overall CIR is a good performance marker and that there was no need to calculate separate performance goals.[91] The conclusion was somewhat easy to reach as they found no difference in CIR among indications contrary to our study where colonoscopy indication ($p<0.001$) affected the CIR (Paper IV: Table 2). Adjusting for case-mix by standardization did, however, have little effect on the CIR. The maximum rank change was eight (compared to 17 in the PDR analysis) and just four endoscopists changed more than five ranks. Two endoscopists were significantly inferior performers according to overall CIR, with endoscopist 29 moving just within 95% CI of the 90% minimum acceptable standard using standardized CIR. The CIR did, however, only change slightly from 82.7% (95%CI 75.6%-88.1%) to 84.7% (95%CI 78.9%-90.5%). The major factor was again few screening colonoscopies (0%). The OR for reaching the cecum in screening colonoscopies was 1.62 (95%CI 1.31-2.01) compared to diagnostic colonoscopies, giving endoscopist 29 a disadvantage in obtaining a high CIR. The disadvantage was, however, far less pronounced than for the PDR analysis. The change in CIR category from "inferior" to "in range" only occurred due to small changes in CIs close to the 90% minimal acceptable standard. (Paper IV: Table 3).

Interpreting a correlation of 0.89 (standardized CIR vs overall CIR) as strong has previously been proposed, but care should be taken when interpreting correlation coefficients.[160] Correlation coefficients provide a single value between [-1;1] that describe the correlation between two variables, but with little information about the underlying distribution of data. Kendall's τ is not sensitive to outliers and heteroscedasticity (slight heteroscedasticity is visible from study IV: Figure 1) but is calculated based on ordinal ranks by comparing concordant and discordant pairs, however there is no information available whether the discordant pairs occur among the highest or lowest ranked endoscopists. A sequential rank agreement method proposed by Ekstrøm et al. allows for a deeper analysis on rank agreement depending on the list depth.[161] Incorporating the method in our analysis would be useful.

Study IV has other limitations. Factors such as previous hysterectomies, visceral adiposity, ethnicity and bowel preparation were not included in the analysis although previous studies found that they could affect either CIR or PDR.[10,162–164] If such variables are distributed unevenly among endoscopists, our case-mix adjustments might be insufficient. The use of PDR instead of ADR does provide an opportunity to "game the system" by removing non-dysplastic polyps. The evidence for PDR/ADR gaming is negligible, but randomly assigning positive polyp findings would lead to non-differential misclassification and bias towards the null hypothesis in relation to patient age, patient gender and colonoscopy indication.[54,165] There might be a higher focus on quality indictors in relation to screening colonoscopies, which could lead to isolated gaming and differential misclassification.

As the study was conducted in a real world setting among multiple endoscopy units, we believe that it is generalizable (externally valid). However, endoscopy units are organized differently in other countries and jurisdictions. The effect of including colonoscopies conducted within the gastroenterology jurisdictions is unclear. Adding another category to the "indication" variable is likely a viable solution. The developed R programme can easily be extended to include additional variables and categories to ensure that overall CIR is reliable in other settings. The provided R programme is available in an open file repository and free to use and modify.[105] It allows for calculation of overall and standardized performance indicators with customizable performance goals. Outputs are generated in R markdown, examples are available in the file repository.[105,166]

CHAPTER 6: CONCLUSION

By investigaing four aspects of colonoscopy quality, we arrive at the following conclusions.

PCCRC-3yr rates are higher in Denmark than in the English NHS and Sweden. This is concerning since 75-86% of PCCRCs are considered avoidable.[8,167,168] By 2012, the Danish PCCRC-3yr rate was at 7.9%, yet falling over time, indicating better colonoscopy quality. We found that PCCRC was associated with right-sided tumour, small tumour size, diverticulosis, hereditary CRC, ulcerative colitis and high comorbidity.

Training programmes for junior and senior endoscopists combined with a colonoscopy quality monitoring system were effective in improving CIR from 87.1% to 92.1% from 2015 to 2019. PDR also increased from 33.7% to 41.7%, but this increase was insignificant in the multivariable analysis. An endoscopist monitoring system based on an SFI within the EHR now provides biannual individual endoscopist feedback in the North Denmark Region.

The overall AE rate of colonoscopies in the North Denmark Region is 1:100 colonoscopies with a fatal AE rate of 1:5000 colonoscopies. Bleedings and perforations were at a rate comparable to the minimal acceptable standards from the UK. Non-procedure-related AEs such as “cardiovascular” and “other” AEs also occurred, indicating that a combination of bowel preparation, sedation or the procedure itself might cause AEs, especially in susceptible individuals.

Standardizing performance markers are useful to investigate the effect of different endoscopist case-mix. Standardizing had a small effect on the CIR and a more pronounced effect on the PDR. Overall CIR are a reasonable performance marker, but care should be taken when interpreting significant inferior performers. Standardization improved the PDR for some poor performers around 8 percentage point questioning whether overall PDR is reliable.

CHAPTER 7: PERSPECTIVES

We expect the 2018 WEO consensus method to be the future benchmark for calculating PCCRC-3yr rates.[64] The paper describing the WEO consensus method has currently been cited > 50 times, and two nationwide studies from England and Belgium have been published using it, indicating its general acceptance.[69,169] Another key advantage of a common methodology is the relative ease of updating numbers by simply rerunning existing programming upon receiving updated databases. The WEO statement on PCCRC-rating methods also includes recommendations for investigating PCCRC events in EHR using a specific framework (root cause analysis).[64] The first study using this framework to identify causes of PCCRC has recently been published.[168] A project approved by the Danish Patient Safety Authority has been initiated to investigate all PCCRC events in the North Denmark Region from 2010 to 2018 (ID: 31-1521-31). Results should be available in around 6 months and will hopefully provide additional insight informing our understanding of and aiding in the prevention of PCCRC. The WEO consensus method recommends continuous tracking and auditing of PCCRCs.[64] Such a system is currently not in place in the North Denmark Region; however, it can be implemented at a relatively low cost. The ongoing study covers 424 potential PCCRCs over a 9-year period, which indicates that around 50 cases should be investigated annually. Developing and testing the RedCap data capture system is time consuming; still, once completed, it is estimated that 20-25 cases can be evaluated on a daily basis.[104] The last junior doctors scheduled for inclusion in the training programme for junior doctors are currently being enrolled. We expect colonoscopy training programmes to continue beyond the present programme, but there are regional upcoming challenges that must be addressed in this respect. Lack of certified trainers remains a challenge as few surgeons seem willing to dedicate themselves to lower-GI endoscopy. Nurses trained in lower-GI endoscopy are currently performing a large proportion of the colonoscopies. It will likely become necessary to include them in the training of junior doctors to secure a sufficient supply of trainers and training colonoscopies in the future. Initiatives attempting to introduce nationwide training programmes are appearing. A national multiregional working group has created a report on future colonoscopy training that has been approved by the Board of the Danish Surgical Society and the Board of the Danish Society for Gastroenterology. This working group will play a part in future negotiations with the Danish Regions and the Danish health authorities and hopefully lead to improvements in future training and generate renewed interest in lower-GI endoscopy. We also hope to see future certification of endoscopists to ensure competence. The certification process itself warrants further consideration. A system similar to the UK-developed Joint Advisory Group accreditation for endoscopy units and certification for individual endoscopists is effective, but the complete setup is relatively complex.[170,171] The development of automated colonoscopy scores is progressing; and if a relationship between recognized performance indicators and automated colonoscopy scores can be established, the accreditation process might be simplified.[172–175]

Continuous tracking of AEs revealed procedure-related colonoscopy complications in the North Denmark Region to be around the minimum standard set by UK quality assurance guidelines.[50] We hope that additional training and upcoming courses addressing polypectomy techniques can move rates towards the UK aspirational target. Inclusion of histopathology would be highly beneficial to evaluate the risk of perforation and bleeding for the individual endoscopist. Study III indicates that colonoscopy can cause both serious and fatal AEs beyond bleeding and perforations. Unfortunately, we were unable to calculate RRs as we had no group for comparison. Uploading a dataset with our confirmed AEs to Statistics Denmark (if approved by the Danish Patient Safety Authority) would provide the opportunity to establish matched comparator groups. Current guidelines recommend continuous tracking of colonoscopy AEs. Our 1,141 potential AEs took place over a 4-year period, indicating that around 300 cases need to be evaluated annually. Currently, a physician can evaluate 40-50 cases daily using the existing RedCap data capture system. The decision to implement continuous monitoring of AEs is pending.

A new EHR is set to be implemented in the North Denmark Region by 2022. The EHR system is currently in place in the Central and Southern Denmark Region. We plan to develop a new, simplified SFI using experiences from the existing SFI and hopefully make it possible for the endoscopists to log in using the BI portal and track their key performance indicators.. Inclusion of histopathology by changing measurement from PDR to ADR is recommended by most guidelines. It remains unclear if histopathology can be automatically incorporated in feedback reports in the upcoming EHR system. If not, matching outputs from the SFI and histopathology system by CPR number, procedure codes and date would be an alternative solution. Another viable solution could be to extend the monitoring conducted by the Danish CRC screening programme to include individual performance tracking on all colonoscopies. Data could be used to create a nationwide colonoscopy database similar to the Norwegian Gastronet or the UK National Endoscopy Database.[77,176]

Regionally, the multiple colonoscopy quality initiatives seem to have improved colonoscopy quality, at least measured by CIR. However, work remains to be done to comply with the latest ESGE and WEO guidelines in relation to monitoring of PCCRC, AEs and the incorporation of histopathology. Other local issues should probably also be addressed, especially in relation to the around 40 endoscopists with < 50 procedures per 6 months. A standard protocol for handling underperformers is also warranted. For now, relatively simple measures might help reduce PCCRC rates by ensuring that patients with the highest risk of PCCRC undergo endoscopy by experienced endoscopists.

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SUPPLEMENTARY TABLES

Supplementary table A Data collected from the supplementary file (SFI)

Name of input field	First level	Second level
Screening colonoscopy?	☐ Yes ☐ No	
Procedure timing[1]	☐ Start time: ☐ Max depth time: ☐ End time:	
Cecum or an ileocolic anastomosis reached?	☐ Yes	☐ Intubation of the small intestine ☐ Visualization of the ileocecal ☐ Visualization of the appendix ☐ Ileocolic anastomosis
	☐ No	☐ Bowel preparation ☐ Pain ☐ Stenosis ☐ Impassable bend ☐ Complications ☐ Instrument failure ☐ No indication of reaching the cecum ☐ Other
Bowel preparation	☐ Excellent ☐ Adequate ☐ Poor ☐ Unacceptable	
Nurse-reported	☐ No discomfort ☐ Minimal discomfort ☐ Mild discomfort ☐ Moderate discomfort ☐ Severe discomfort	
Sedation	☐ No sedation ☐ Sedated ☐ General anaesthesia	

Continues on the next page

Continued from the preceding page

Colonoscopy	☐ Normal colonoscopy	
	☐ Biopsies from suspected tumour	
	☐ Biopsies from suspected inflammatory bowel disease	
	☐ Diverticula	
	☐ Polyps	[*number*] of identified polyps [*number*] of removed polyp [*number*] polyps sent for examination by the pathologist
Notes	[free text field]	

[1]Current time/date are inserted when clicking the box or by manual entry.
☐: "click box", [number]: Value from 0-99; [free text field]: Up to 200 characters.
Note: Patient age and patient sex are collected automatically from EMR. Second-level selections are only available with the corresponding first-level selection.

Supplementary table B Endoscopy units defined as outpatient units

Unit code	Name
7603116	Thy kirurgisk dagafdeling
760311E*x*	Thy tarmkræftscreening
8001126	Hob Kirurgisk Sammedagskirurgi
8001129*x*	Alb Mave-Tarmkirurgisk Amb.
8001289	Alb Med Gastroenterologisk Amb
800112E*x*	Tarmkræftscreening
8001609	Far Medicinsk Ambulatorium
8003079*x*	Hjr Kirurgisk Amb.
800307D*x*	Frh Kirurgisk Dagafdeling
800307E*x*	Frh Tarmkræftscreening
8003209	Hjr Medicinsk Ambulatorium
800309E	Ven Tarmkræftscreening

Unit codes ending with "*x*" includes additional subcategories

Supplementary table C Baseline characteristics of the 2015 quality survey at Aalborg University Hospital

Endoscopist	Colonoscopies *n*	Patient age Mean (95% CI)		CIR (%) Mean (95% CI)		PDR (%) Mean (95% CI)		Patient sex: Male (%) Mean (95% CI)		Indication Screening (%) Mean (95% CI)	
A	123	62	(60-65)	87	(80-92)	20	(14-29)	49	(40-58)	1	(0-4)
B	96	63	(60-66)	81	(72-88)	26	(18-36)	47	(37-57)	5	(2-12)
C	85	65	(62-68)	74	(63-83)	22	(14-33)	47	(36-58)	18	(10-27)
D	83	62	(60-65)	93	(85-97)	27	(17-37)	48	(37-59)	2	(0-8)
E	81	63	(61-66)	96	(90-99)	46	(35-57)	53	(42-64)	51	(39-62)
F	62	61	(57-65)	87	(76-94)	40	(28-54)	50	(37-63)	6	(2-16)
G	49	67	(64-70)	92	(80-98)	37	(23-52)	47	(33-62)	29	(17-43)
H	47	64	(60-68)	83	(69-92)	45	(30-60)	40	(26-56)	47	(32-62)
I	43	64	(60-67)	86	(72-95)	56	(40-71)	72	(56-85)	70	(54-83)
Low vol. (n: 20-40)	98	64	(62-66)	88	(80-94)	38	(28-48)	44	(34-54)	53	(43-63)
Very low vol. (n < 20)	127	62	(60-64)	91	(84-95)	38	(29-47)	49	(40-58)	25	(18-34)
	894	**63**	**(62-64)**	**87**	**(85-89)**	**34**	**(31-37)**	**49**	**(46-52)**	**24**	**(22-27)**

CIR: Cecum intubation rate. PDR: Polyp detection rate

Supplementary table D Logistic regression for not reaching the cecum in the 2015 quality survey

	OR	95% CI	p-value
Endoscopist			
A	3.02	0.83 - 11.00	0.09
B	4.69	1.29 - 16.98	< 0.05
C	7.26	2.04 - 25.85	< 0.01
D	1.59	0.37 - 6.73	0.53
E	1.00		
F	3.24	0.80 - 13.10	0.10
G	1.82	0.38 - 8.64	0.45
H	5.41	1.33 - 21.92	< 0.05
I	5.08	1.17 - 21.93	< 0.05
Low vol (n= 20-40)	3.89	1.05 - 14.43	< 0.05
Very low vol (n < 20)	2.44	0.66 - 9.04	0.18
Age group			
<50	0.25	0.10 - 0.63	< 0.05
50-59	0.65	0.36 - 1.16	0.18
60-69	1.00		
70-79	0.93	0.55 - 1.56	0.15
>79	1.57	0.80 - 3.08	0.19
Indication			
Screening	1.00		
Diagnostic	2.09	1.11 - 3.96	< 0.05
Sex			
Female	1.00		
Male	1.00	0.67 - 1.51	0.98

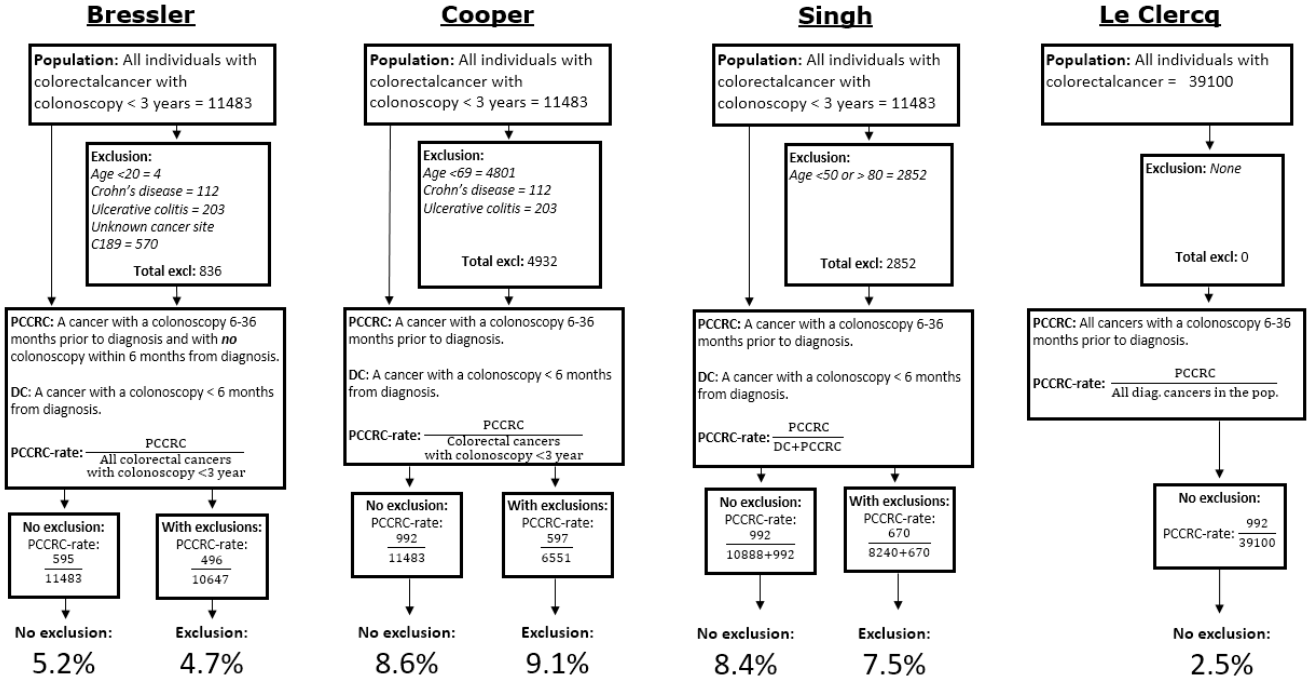
OR: Odds Ratio

Supplementary table E Logistic regression for finding at least one polyp in the 2015 quality survey

	OR	95% CI	p-value
Endoscopist			
A	1.15	0.57 - 2.32	0.69
B	1.53	0.75 - 3.10	0.24
C	1.00		
D	1.62	0.78 - 3.36	0.20
E	2.08	1.02 - 4.25	< 0.05
F	2.92	1.38 - 6.17	< 0.01
G	1.74	0.78 - 3.91	0.18
H	2.27	1.01 - 5.11	< 0.05
I	2.46	1.06 - 5.67	< 0.05
Low vol (n= 20-40)	1.49	0.75 - 2.99	0.26
Very low vol (n < 20)	2.11	1.10 - 4.05	< 0.05
Age group			
<50	1.00		
50-59	1.68	1.74 - 3.00	0.08
60-69	2.46	3.21 - 4.27	< 0.01
70-79	2.73	3.53 - 4.75	< 0.01
>79	2.92	2.97 - 5.92	< 0.01
Indication			
Diagnostic	1.00		
Screening	2.97	2.01 - 4.40	< 0.01
Sex			
Female	1.00		
Male	1.54	1.14 - 2.07	< 0.01

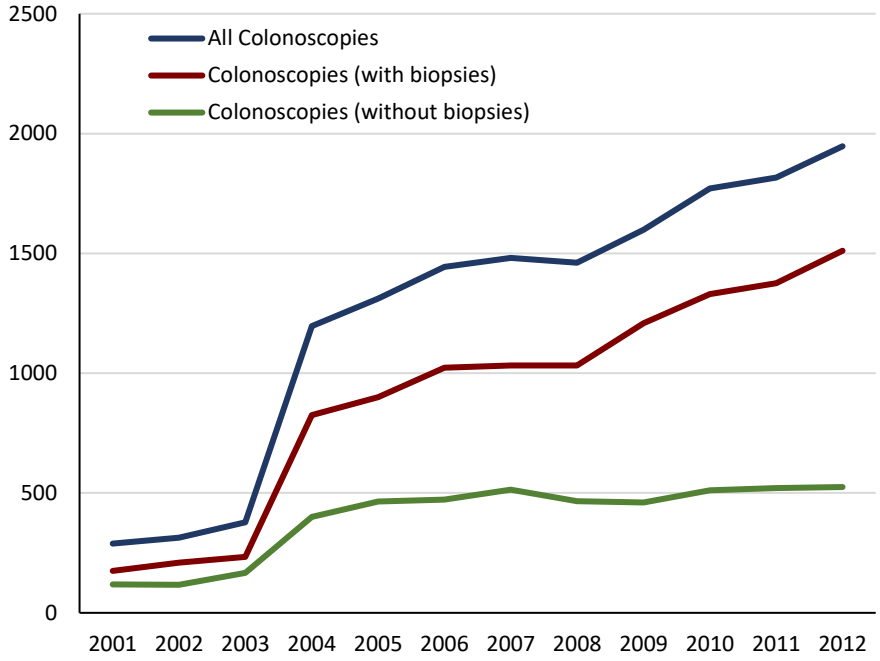
OR: Odds Ratio

SUPPLEMENTARY FIGURES



Supplementary figure A Calculation of Danish PCCRC-3yr from 2001-2010 using four different methods

Diagnosed Cancer, PCCRC: Post Colonoscopy Colorectal Cancer, CRC: Colorectal Cancer, C189: Malignant neoplasm of the colon, unspecified. Flowchart modified from Morris E. et al.



Supplementary figure B Numbers of annually diagnosed cancers (DC) by colonoscopy.

From Pedersen et al: Risk of post-colonoscopy colorectal cancer in Denmark: time trends and comparison with Sweden and the English National Health Service

ISSN (online): 2246-1302
ISBN (online): 978-87-7210-809-4

AALBORG UNIVERSITY PRESS