

## **Publications with particular relevance for the colorectal screening program**

Update 1<sup>st</sup> November 2023

### **2023**

1. Botteri E, Peveri G, Berstad P, et al. Changes in Lifestyle and Risk of Colorectal Cancer in the European Prospective Investigation Into Cancer and Nutrition. *The American Journal of Gastroenterology*. 2023 Apr;118(4):702-711. DOI: 10.14309/ajg.0000000000002065. PMID: 36227801.

#### **Changing from a "bad" to a "good" lifestyle (as measured by the Healthy Lifestyle Index - HLI) reduced the risk of bowel cancer by 22%.**

This study is the result of a European collaboration in the project "European Prospective Investigation into Cancer and nutrition" - also known as the "EPIC" study. Diet and other parts of the lifestyle (including smoking and exercise) were recorded with an approx. six years' gap from baseline to a second round of questionnaires among approx. 300,000 individuals from 10 European countries. Participants were aged 30-70 years at the start of the study. Data were compressed into a lifestyle score ("Healthy Lifestyle Index - HLI") which ranged from 0 (worst) to 16 (best). Eight years after the last round of registrations, 2,800 of the 300,000 had developed large bowel cancer.

Those who had improved their HLI score by 3 or more had a 22% reduced risk of developing bowel cancer in the next 8 years. Those who had worsened their HLI score had a correspondingly increased risk of bowel cancer. This study suggests that even in mid-life adulthood it is not too late to improve lifestyle to obtain a health benefit.

2. Bucher-Johannessen C, Birkeland EE, Vinberg E, Bemanian V, Hoff G, Berstad P, Rounge TB. Long-term follow-up of colorectal cancer screening attendees identifies differences in *Phascolarctobacterium* spp. using 16S rRNA and metagenome sequencing. *Frontiers Oncology* 2023;13:p.1183039

#### **Investigation into whether analyzes of intestinal bacterial flora can be developed into a new screening method against bowel cancer.**

The Norwegian Colorectal Cancer Prevention study (NORCCAP) is an investigation where approx. 21,000 people aged 50-64 years, living in Oslo or Telemark County, were offered a screening examination in 1999-2001 for the detection of bowel cancer and possible precursors to bowel cancer (polyps). Prior to the screening examination, stool samples were frozen and stored in a biobank with a view to develop new and better screening methods than what we had at the time.

Intestinal bacteria are thought to be important for the risk of developing bowel cancer – some probably with protective properties (reduced cancer risk), but some bacteria may be associated with an increased risk of bowel cancer. There are more bacteria in the gut than we have cells in the body. Technologically, it has not been possible to separate the different bacteria from each other (by cultivating the bacteria) until we now in recent years have developed molecular methods (gene identification) to identify and characterize bacteria. Thus, we have been able to use biobanked stool samples stored since 1999-2001 to look at the risk of bowel cancer since 2001, i.e. during approx. 17 years of follow-up after sampling.

In this study, we examined stored stool samples from a total of 144 individuals who had either developed bowel cancer during the follow-up period, or diagnosed and removed high-risk polyps at the screening examination or who had not developed cancer during 17 years of follow-up. There were small differences between these three groups in the composition of the intestinal bacterial flora. Certain bacteria occurred more frequently among those who later developed bowel cancer,

but the patient sample was small and we are still far from having a "bacteria-based" screening method. The research continues with larger and other patient samples where the storage methods for the biobank material are better than it has been in NORCCAP.

3. *Bresalier RS, Senore C, Young GP, Allison J, Benamouzig R, Benton S, Bossuyt MM, Caro L, Carvalho B, Chiu HM, Coupé VMH, de Klaver W, de Klerk CM, Dekker E, Dolwani S, Fraser CG, Grady W, Guittet L, Gupta S, Halloran SP, Haug U, Hoff G, Itzkowitz S, Kortlever T, Koulaouzis A, Ladabaum U, Lauby-Secretan B, Leja M, Levin B, Levin TR, Macrae F, Meijer GA, Melson J, O'Morain C, Parry S, Rabeneck L, Ransohoff DF, Sáenz R, Saito H, Sanduleanu-Dascalescu S, Schoen RE, Selby K, Singh H, Steele RJC, Sung JY, Symonds EL, Winawer SJ, Members of the World Endoscopy Colorectal Cancer Screening New Test Evaluation Expert Working Group. An efficient strategy for evaluating new non-invasive screening tests for colorectal cancer: the guiding principles. Gut 2023;72:1904-18.*

**Screening for bowel cancer: Guidelines for how to meet the need for testing new screening methods within reasonable timeframes.**

Colon cancer screening has become an established health service in many countries. In the USA alone, approx. 14 million screening colonoscopies are performed each year. Most countries use screening methods to detect invisible blood in the stools before a detection of blood leads to a colonoscopy examination of the bowel. In Norway, the roll-out of a national screening program started in 2022. The aim of such programs is to reduce the incidence of bowel cancer and death due to bowel cancer. It takes an average of 10-15 years from the time a benign polyp can be detected until the polyp has possibly developed into cancer. NB! Very few of the common polyps (wart-like growths) in the intestine turn into cancer.

New, promising screening methods are constantly being developed, but they must eventually be tested as part of an ongoing screening program - preferably in a randomized study where the "new test" is tested against the "current standard". When the goal of reducing the incidence and death of bowel cancer lies 10-15 years into the future, few people will accept to wait that long to find out if the goal has been reached with the new method.

In this project, a group of experts from all over the world have tried to find acceptable methods for testing new screening methods without having to wait 10-15 years before a decision can be made whether or not the new test is better than the current standard. The article is intended as a guide on how to solve the problems when there is a need for adequate testing of new screening methods and at the same time prevent decision-makers from being tempted to skip the need for proper testing.

4. *Birkeland E, Ferrero G, Pardini B, Umu SU, Tarallo S, Bulfamante S, Hoff G, Senore C, Rounge TB, Naccarati A. Profiling small mRNA in fecal immunochemical tests: Is it possible? Molecular Cancer 2023;22:161*

**Technically possible to detect microRNA after many years of frozen storage. Important for the search for better screening methods for bowel cancer screening.**

RNA (ribonucleic acid) are molecules that are needed for most biological processes in interaction with the genetic material DNA, which has the "recipe" for all the processes. MicroRNAs are small pieces of RNA - molecules consisting of only 21-23 nucleotides. Nucleotides are molecules made up of nitrogen, phosphate and different types of sugar. MicroRNAs have no direct coding function, but can indirectly influence the production of proteins and genetic material in all types of cells – even bacterial cells. Research is underway to identify microRNA that can be used as a biomarker and a possible screening method for bowel cancer. The most common screening method for screening for bowel cancer is currently screening for invisible blood in the stools.

In this study, we have examined stool samples that have been frozen for up to 17 years in different ways in screening projects in Norway and Italy to investigate the durability of microRNAs from the bacterial flora in the gut when frozen under different conditions. The answer to the question of whether it is possible to use stored excess material from intestinal screening for blood in stool for research into microRNA-based new screening methods is "yes, it is possible". It is important to be able to use material that has been obtained perhaps many years before cancer occurs if you are looking for screening methods that can detect possible precursors to cancer - in other words detect lesions which carry a high risk of turning into cancer BEFORE they turn into cancer.

5. Hoff G. **Humpete vei til tarmscreening** [A bumpy road to bowel screening. In Norwegian]. *Norsk Gastroforenings Bulletin (NGF-nytt) 2023;30:26-28*

The screening programs for cervical and breast cancer are well established in Norway. The EU recommended screening for bowel cancer as early as 2003. In Norway, the roll-out of the national screening program against bowel cancer began in 2023. We thus started a bowel screening program rather late, but we have used the time well and contributed significantly with research on the topic - in altogether more than 250 scientific publications and more than 30 doctoral theses.

This article presents a short version of the path from the idea of a bowel screening program via research into screening methods and colonoscopy techniques, creation of a national quality assurance program (Gastronet), development of ICT solutions (including a countrywide EMR for colonoscopies with automatized reporting to for quality assurance) and up to the rollout of the screening program.

## 2022

6. Ribe SG, Botteri E, Løberg M, Randel KR, Kalager M, Nilsen JA, Gulichsen EH, Holme Ø. *Impact of time between faecal immunochemical tests in colorectal cancer screening on screening results: A natural experiment. Internat J Cancer 2023;152:1414-24*

**The proportion of screenees diagnosed with bowel cancer in their next screening round is very low among those who had not even a trace of blood detected in the previous round of stool testing.**

The study is part of the pilot study on colon cancer screening where we look at the interval between two screening examinations measuring the amount of invisible blood in stool samples by FIT (faecal immunochemical test). FIT is performed every 2 years. If the sample shows >15 mcg Hb/g faeces, then the test is considered positive and the participant is referred to have a work-up colonoscopy examination. In case of a negative FIT result (no blood or <15 mcg Hb/g faeces), small amounts of invisible blood can still be measured below the threshold value. We looked at the interval between two FITs in 18,522 participants with a negative first FIT, with randomly distributed variation in screening interval from 1.5-3.5 years. The proportion of positive samples at the next FIT increased slightly with increased time intervals in both groups, but the proportion of positive samples was still low up to a 3.5 year interval between 1<sup>st</sup> and second screening round. However, we found that the group with no detectable sub-threshold blood in 1<sup>st</sup> round had a low proportion of cancer at the next examination (0.09 %), while cancer cases were found twice as frequently in those who had invisible sub-threshold blood in the 1<sup>st</sup> round (0.28 %).

7. *Kværner AS, Birkeland E, Vinberg E, Hoff G, Hjartåker A, Rounge TB, Berstad P. Associations of red and processed meat intake with screen-detected colorectal lesions. Br J Nutr. 2022 Sep 7;129(12):1-11. doi: 10.1017/S0007114522002860. Epub ahead of print. PMID: 36069337; PMCID: PMC10197083.*

#### **A high intake of red and processed meat increases the risk of bowel cancer**

On 22 August 2022, the national bowel screening program was launched. Prior to this, there have been two large pilot projects testing screening methods - the first was in Telemark County and Oslo City 1999-2001 and the second in Østfold County and Vestre Viken started in 2012 [in the final phase now in 2023]. Both of these projects also contained sub-projects on possible associations between lifestyle and cancer. This sub-project is from the last of these two pilot projects:

Among those who had a positive screening test for invisible blood in their stools (which required a work-up colonoscopy) during a screening examination, approx. 1,600 filled in a 14-page questionnaire designed to estimate daily food and drink intake - in addition to information about lifestyle (smoking and exercise habits). The questionnaire was filled in before they had a work-up colonoscopy due to testing positive for blood in the stools using a colonoscope (flexible "intestinal scope" for examination of the entire colon). Only 2% of participants consumed less than the recommended upper limit of 21 g of processed meat per week. 27% of those examined had "advanced lesions" in the intestine, i.e. cancer or high-risk polyps, the latter implying a high risk of developing into cancer.

Advanced lesions were associated with a high intake of red and processed meat - also when statistically corrected for sex, age, smoking and exercise habits. Low and moderate intake produced no increased risk. This is a large study with very good data collected before the participants had a colonoscopy and were made aware of any lesions in the bowel. The findings are in line with previous studies which have also indicated a connection between bowel cancer and a high intake of red and processed meat.

This type of research should be incorporated into ongoing screening programs in order to obtain data FROM the target group and show results that are thus relevant in particular FOR the target group for screening. Although bowel screening is about detecting cancer and possible precursors to cancer, it may also be the best opportunity and an ideal "window of opportunity" to reach out with advice on healthy lifestyle.

8. *Hoff G, Botteri E, Berstad P, Randel KR. Norway – a retarded country close to 20 years since EU recommended colorectal cancer screening? A failure or a success? Norsk Epidemiologi 2022;830:83-86*

#### **What have we achieved by starting bowel cancer screening almost 20 years after the EU's recommendation?**

The European Union recommended already in 2003 that member states should consider starting bowel cancer screening. Norway started rolling out its bowel cancer screening programme in autumn 2022 – almost 20 years later – even though there are few countries in the world which have a higher incidence of bowel cancer than Norway. Introduction of national screening programmes such as screening against cervical cancer, breast cancer and now bowel cancer has often been introduced in several countries more because of political beliefs and good intentions than solid, scientific evidence.

In this article, published in connection with the Cancer Registry's 70<sup>th</sup> anniversary, we have explained what we in Norway have achieved during this 20-year "waiting period" - largely despite

the lack of support for the most important studies. During this period, more than 160 original scientific articles and 20 PhD's have emerged from our and related research groups. This may have contributed to being well equipped for planning a scientifically sound bowel screening program. We have gained an increased understanding and conviction that research must be a continuous integral part of this screening program in order for it to develop into an ever better health service.

9. Juul FE, Cross A, Schoen R, Senore C, Pinsky P, Miller E, Segnan N, Wooldrage K, Wieszczy-Szczepanik P, Armaroli P, Garborg K, Adami HO, Hoff G, Kalager M, Bretthauer M, Løberg M, Holme Ø. 15-year benefits of sigmoidoscopy screening on colorectal cancer incidence and mortality: a pooled analysis of randomized trials. *Ann Intern Med* 2022;175:1525-33

**Combined research data from several countries show that sigmoidoscopy screening may reduce both the incidence and death of bowel cancer by approx. 20%**

The world's first randomized study on bowel screening was carried out in Telemark in 1983. Randomization means that people are drawn by lottery into either a group that is offered screening or a group that receives "standard health care", i.e. no screening. The screening method to be tested was examination of the lower approx. 50 cm of the large intestine using a flexible, thin "intestinal scope" for visualization of the internal lining of the bowel. Since then, the method has been used in larger randomized studies in several countries, e.g. the NORCCAP project in Telemark County and City of Oslo 1999-2001.

In the article that has now been published, the results are collected from four large randomized studies in the USA, Great Britain, Italy and Norway (NORCCAP) - a total of 274,952 people equally divided between screening and control groups. In Norway, the target group was drawn directly from the National Population Register because that is how it will be done in a national screening programme. In the other countries, the target group was first asked if they were willing to be randomized and only those expressing willingness to participate were then randomized. Attendance in Norway was 65%.

15 years after sigmoidoscopy, both the incidence of bowel cancer and death due to bowel cancer were reduced by approx. 20% among those who were invited to screening compared to the control group. The incidence was reduced by 25% among men and 16% among women. Death due to bowel cancer was reduced by 27% for men, while there was no statistically significant reduction among women. This year (2022) saw the start of the rollout of the Bowel Screening Program in Norway. This screening programme is currently based on testing for invisible blood in the stools, but with a possible transition to change to primary colonoscopy screening in years to come, i.e. using a "bowelscope" examination of the entire large bowel - not just sigmoidoscopy (which may be considered a "half-way colonoscopy").

10. Bretthauer M, Løberg M, Wieszczy P, Kalager M, Emilsson L, Garborg K, Rupinski M, Dekker E, Spaander M, Bugajski M, Holme Ø, Zauber AG, Pilonis ND, Mroz A, Kuipers E, Hernan MA, Adami HO, Regula J, Hoff G, Kaminski MF. Effect of colonoscopy screening on risks of colorectal cancer and related death. *NEJM* 2022;387:1547-56

**Colon cancer screening with colonoscopy may be less effective than expected**

The official opening of the national bowel screening program was in August 2022. The screening method chosen is to examine for invisible blood in the stools using an immunochemical test for human blood in the stools (Fecal Immunochemical Test - FIT) – a test which does not detect blood from e.g. an ingested bloody beef. Eventually, the idea is to replace FIT with primary colonoscopy screening, i.e. examination of the entire large bowel with a flexible, thin "intestinal scope".

Colonoscopy is considered the "gold standard", i.e. the best method, when patients with bowel symptoms are recommended to have an examination of their large bowel. The idea of colonoscopy as a screening offer has therefore been the very best - to offer the "gold standard" straight away - not just as an investigation when other types of screening method have yielded a positive test result, e.g. by detection of invisible blood by FIT. A colonoscopy can, in addition to detecting bowel cancer before it has caused symptoms, also detect and remove benign growths (polyps) in the intestinal mucosa – i.e. lesions that in a few cases may turn into cancer, and thus prevent the development of cancer.

The NordICC project (Nordic-European Initiative on Colorectal Cancer) is a collaboration between several European countries - coordinated from Norway. About 85,000 people aged 55-64 years were drawn by lottery from population registers for screening with colonoscopy or no screening. After 10 years, the results now show that the risk of getting bowel cancer was reduced by 18% among those who were invited to screening compared to the control group. Overall attendance was only 42% - 33% in Poland, which contributed with 64% of those invited to screening and 61% attendance in Norway, which contributed with 31% of those invited. With the inclusion of almost twice as many Poles as Norwegians, the results are strongly influenced by the low attendance in Poland. The overall reduction in bowel cancer was thus 16% in Poland, but 24% in Norway. Even so, this is somewhat lower than expected. Good attendance is naturally a prerequisite for a screening program to be successful. Now it is also shown for colonoscopy screening.

11. Pedersen IB, Rawa-Golebiewska, Calderwood AH, Brix LD, Grode LB, Botteri E, Bugajski M, Kaminski MF, Januszewicz W, Ødegaard H, Kleist BA, Kalager M, Løberg M, Bretthauer M, Hoff G, Medhus AW, Holme Ø. Complete polyp resection with cold versus hot snare polypectomy for polyps sized 4-9 mm: A randomized controlled trial. *Endoscopy* 2022;54:961-9

**Using a "cold" sling is not equivalent to using a "hot" sling when removing polyps in the intestine.** Some polyps (wart-like growths on the intestinal lining) may develop into bowel cancer. Removal of these lesions is therefore desirable to reduce the risk of bowel cancer. This is done through a colonoscope (a thin, flexible "intestinal scope" that is inserted through the back passage). Polyps measuring 4-9 mm in diameter can be removed by placing a snare ("lasso") around the polyp. The snare can be electrically conductive ("hot") to coagulate and reduce the risk of bleeding - or non-conductive ("cold") since the risk of bleeding is very small when removing polyps smaller than 10 mm with the snare.

In this study, 425 patients with a total of 608 polyps were drawn by lottery to have the polyps removed with a hot or cold snare. There were 5 (1.2%) cases of bleeding due to the polyp removal and all were treated during the colonoscopy itself – one in the warm snare group and 4 in the cold snare group. Tissue samples from the marginal zone of the mucosa where the polyp had been removed showed that 34 (10.7%) of 318 polyps in the cold snare group were not completely removed compared to 21 (7.4%) of 283 polyps when removed with a hot snare. The difference was statistically significant. The hypothesis that the use of a cold snare is just as good as a hot snare could therefore not be confirmed in this study.

## 2021

12. Knudsen MD, Hoff G, Tidemann-Andersen I, Bodin GE, Øvervold S, Berstad P. Public Awareness and Perceptions of Colorectal Cancer Prevention: a Cross-Sectional Survey. *J Cancer Educ.* 2021 Oct;36(5):957-964. doi: 10.1007/s13187-020-01721-5. PMID: 32112366; PMCID: PMC8520865.

Bowel cancer is largely considered to be a lifestyle disease associated with a westernized lifestyle. Norway ranks very high in the statistics of countries with most cases of bowel cancer. It is planned to start a nationwide bowel screening program in Norway in 2022, where cohorts of men and women are offered screening for invisible blood in the stools every two years (5 rounds in total) starting in the year they turn 55 years (approx. 75,000 in each age cohort). It is therefore interesting to survey people's knowledge of bowel cancer, attitudes towards screening and lifestyle and which sources of information the target group for screening rely mostly on during the next few years.

In this survey, 4,375 people aged 39-55 were randomly drawn from the database of Kantar AS (the agency for Gallup surveys) and asked a number of questions about, among other things: What is screening; how likely is it that you will participate in screening for bowel cancer; why do you choose to participate/not participate; how do you consider your own knowledge of risk factors for bowel cancer; from which sources would you prefer to obtain information about risk reduction. 46% answered the questionnaire

Among those who answered, more than half of them did not even know what screening was (54%). Still, 87% presumed that they would participate in the imminent screening programme. 91% stated that the prospect of detecting any cancer early would be the most important motivation for wanting to participate. 68% would like to receive information on how the cancer risk could be reduced. The Directorate of Health, the Cancer Society and the General Practitioner were stated as the three preferred and most trustworthy sources of information. The authors conclude that advice on cancer-preventive lifestyle should be included as part of the screening programme.

13. *Pedersen IB, Bretthauer M, Kalager M, Løberg M, Hoff G, Matapour S, Hugin S, Frigstad SO, Seip B, Kleist B, Løvdal L, Botteri E, Holme Ø. Incomplete endoscopic resection of colorectal polyps: a prospective quality assurance study. Endoscopy 2021;53:383-91*

Colonoscopy is an examination of the colon and rectum with a flexible "intestinal scope". Detection and removal of polyps by colonoscopy reduces the risk of future bowel cancer. The polyps are usually removed with a wired snare ("lasso") which is inserted through the colonoscope and placed around the polyp. Electricity is often used to cauterize the polyp, but the snare can also cut the stem or base of the polyp without the use of electricity. In this project, the removal of 327 polyps in 246 patients was examined to estimate the effectiveness of snaring polyps. 54 polyps (16%) were not completely removed. These were most often (and as expected) flat polyps without a clear "stem" and polyps localized proximally (in the innermost part) in the large bowel. Between the doctors who performed the colonoscopies, there was no statistical difference in their performance results.

Formal training of colonoscopists and continuous quality assurance of colonoscopy performance is important. The type of polyps that were most often incompletely removed were so-called flat, "serrated" polyps in the uppermost parts of the large bowel. It is not clear how important it is to have this type of polyp removed in order to prevent future bowel cancer. It is possible that these serrated polyps are just markers for a generally increased risk of bowel cancer and that further colonoscopy checks are most important for these patients.

14. *Knudsen MD, Botteri E, Holme Ø, Hjartåker A, Song M, Thiis-Evensen E, Hoff G, Berstad P. Association between lifestyle and site-specific colorectal lesions in screening with faecal immunochemical test and sigmoidoscopy. Dig Liver Disease, 2021;53:353-9*

A national bowel cancer screening program is planned to start in 2022. Since 2012, we have had a study running in Østfold County and Vestre Viken as a pilot of such a program. In this study,

140,000 participants have been drawn by randomization from the population register to be offered either screening with sigmoidoscopy (a camera on the tip of a flexible tube to examine the lower approx. 50cm of the intestine) or testing for invisible blood in the stools (FIT - a "Fecal Immunochemical Test", which gives a positive test result only for human blood – not for dietary blood from e.g. a juicy steak).

This part of the pilot study includes all 14,842 people who were invited for screening in the period November 2012 to September 2013. They also filled in a questionnaire about lifestyle, including smoking, alcohol, exercise, diet. This provided the basis for a score for "unhealthy lifestyle". The objective was to see if any factors and "lifestyle scores" could be predictive for findings at colonoscopy after a positive screening test and whether the findings (polyps and cancer) could be expected to be found far down or far up in the large bowel (i.e. out of reach of sigmoidoscopy) and whether this can provide a basis for a more individualized and tailored screening option. "Advanced lesions", i.e. cancer or polyps with an increased risk of turning into cancer, were found more frequently in the upper part of the colon in those who smoked, had a high alcohol intake and were overweight. This study may indicate that a full large bowel examination with primary colonoscopy screening (not just a "half-way" sigmoidoscopy) can be a cost-effective screening method for people with a high score for "unhealthy lifestyle". However, larger studies with a slightly different design are needed before conclusions can be drawn.

15. Hoff G, Botteri E, Huppertz-Hauss G, Kvamme JM, Holme Ø, Aabakken L, Dahler S, Medhus AW, Blomgren I, Sandvei P, Darre-Næss O, Kjellevoid Ø, Seip B. **The effect of train-the-colonoscopy-trainer course on colonoscopy quality indicators.** *Endoscopy*, 2021;53:1229-34

**Background:** Since 2014, the Endoscopy School has offered hospitals and private centers to send representatives to a Colonoscopy Instructor Course (KIK) at the Endoscopy School. The usefulness of training courses is often assessed simply by asking the participants whether they think the course has been useful or not. In this project, the effect of participation in KIK is measured as a change in measurable performance quality of all colonoscopies at the centres – i.e. monitoring the impact on center level of having a well-trained local instructor.

**Material and method:** The database consisted of colonoscopies routinely reported to the national quality register Gastronet 2014-2019 from Norwegian colonoscopy centers - regardless of whether they were represented by course participation or not. The effect was measured collectively for all colonoscopists at the instructors' colonoscopy center in the year before and then in the year after the first year of the center being represented at a KIK. We used three defined quality variables (patient-reported pain, whether the entire colon was completely examined and the proportion of colonoscopies with detection of polyps 5 mm in diameter or larger). The effect of KIK up to 5 years after participation was also estimated. Non-participating colonoscopy centers were assigned a virtual year of participation ("pseudo-participation") for the analyses.

**Results:** Eleven participating centers had registered colonoscopies in Gastronet in the year before and after their first KIK representation with a total of 18,555 colonoscopies. Eleven centers without KIK (but with matched allocation of virtual KIK year) had contributed 10,730 colonoscopies to this analysis. More than 120,000 colonoscopies were included in the analysis of the duration of the effect (up to 5 years). Detection of polyps increased at centers that had sent colonoscopists to KIK courses and this effect persisted over a 5-year period for both male and female patients. Correspondingly, KIK course representation led to a reduction in the proportion of patients with moderate or severe pain during colonoscopy, but only for women – again with a duration of at least 5 years. This is particularly gratifying since women experience pain during colonoscopy more often than men.



**Conclusion:** Participation in KIK can be a useful tool for increasing the quality of colonoscopies at centers that want to increase measurable quality. A similar evaluation of course participation can be considered to be used in other fields of professional training, provided that data are accessible in a quality register like Gastronet. [Dagens Medisin 24.02.2021](#)

16. Kværner AS, Birkeland E, Bucher-Johannessen C, Vinberg E, Nordby JI, Kangas H, Bemanian V, Ellonen P, Botteri E, Natvig E, Rognes T, Hovig E, Lyle R, Ambur OH, de Vos W, Bultmann S, Hjartåker A, Landberg R, Song M, Blix HS, Ursin G, Randel KR, de Lange T, Hoff G, Holme Ø, Berstad P, Rounge TB. **The CRCbiome study: a large prospective cohort study examining the role of lifestyle and the gut microbiome in colorectal cancer screening participants.** *BMC Cancer* 2021;21:1-14 (article 930)

In 2012, a project for piloting a bowel cancer screening program started in Østfold County and Vestre Viken, Norway. 140,000 women and men aged 50-74 have been offered screening with either sigmoidoscopy once-only (examination of the lowermost approx. 50cm of the large bowel with a flexible "intestinal scope") or testing a stool sample for invisible blood every two years. These are good screening methods, but both have their disadvantages and we are looking for other screening methods.

In this article, we describe the plan for an ambitious continuation of this screening pilot project where we will use stool samples to examine the intestinal flora and the possibilities for developing screening methods based on findings in the intestinal flora instead of examining for blood in the stools. This is now made possible thanks to advanced technology (e.g. examining the genetic material to characterize the different types of gut bacteria - not old-fashioned "cultivation" of the bacteria which is hopeless for the thousands of types of bacteria in the gut). The project is also expected to provide insight into changes in intestinal flora over time in relation to diet and lifestyle. 2,700 participants in the trial screening project are planned to be invited to participate in this CRCbiome study. So far, 2,426 participants have been recruited.

## 2019

17. Hoff G, Ursin G, Løberg M, de Lange T, Skovlund E, Holme Ø. **Continuous development of colorectal cancer screening programmes.** *Acta Oncologica* 2019;58:822-3  
[doi:10.1080/0284186X.2019.1588475](#)

Although screening against bowel cancer has been shown to reduce the risk of death due to bowel cancer and in some cases also reduce the risk of developing bowel cancer, we are far from having the ideal screening method. New methods and strategies must therefore be developed further. The EU recommended bowel cancer screening as early as 2003 and most Western countries have introduced or are in the process of introducing screening programmes. This means that all testing of new methods and further development of screening services must take place within the framework of such screening programmes. This is because everyone in the currently eligible screening age is invited to a bowel screening programme and they will not be available for participation in independent research projects on new screening methods.

This article is intended to raise awareness that established screening programmes must actively take responsibility for continuous improvement of the program through research and health authorities must make arrangements to facilitate such. This has proved not to be as easy to achieve as one would expect.

## 2018

18. Rounge TB, Meisal R, Nordby JJ, Ambur OH, de Lange T, Hoff G. **Evaluating gut microbiota profiles from archived fecal samples.** *BMC Gastroenterology* 2018;18:171 doi:10.1186/s12876-018-0896-6

We have as many bacteria in our gut as we have cells in our body, but we know little about these bacteria. Old-fashioned cultivation of intestinal bacteria has major limitations. Mapping of intestinal bacteria has become much better in recent years thanks to the possibilities for molecular analyses, for example examination of genetic material (DNA) in the bacteria.

In various screening projects against bowel cancer, deep-frozen samples of stools have been stored for up to 17 years. With DNA analyzes of the bacteria, we may now be able to find out which bacteria 17 years ago have subsequently been shown to be associated with a later risk of developing bowel cancer. With this DNA technology, we may also be able to find better screening methods. In order to get started with this, we need to find out if stored stool samples can really be used for this type of research. This study concludes that stored stool samples can be used. This leaves room for further research into intestinal bacteria and the risk of bowel cancer.

## 2017

19. de Lange T, Randel KR, Schult A, Knudsen M, Kirkøen B, Jørgensen A, Botteri E, Berstad P, Ursin G, Bretthauer M, Hoff G. **Sigmoidoskopi og testing for blod i avføringen – en sammenlignende screeningstudie.** *Tidsskr Nor Legeforen* 2017;137:727-30

Norway is one of the countries in the world with the highest incidence of large bowel cancer. The numbers have tripled since the 1950s. About 6% of women and 8% of men now get this form of cancer. 5-year survival is approx. 65%. Compared to many European countries with a much lower incidence of bowel cancer, Norway has been slow to introduce bowel cancer screening, but we have been a leader in research into bowel cancer screening.

This article describes piloting of a national screening programme. The pilot is designed as a randomized comparison of screening for invisible blood in the stools compared to screening by sigmoidoscopy (examination of the bottom approx. 50 cm of the intestine with a flexible "intestinal scope"). The first screening round started in 2012 and is expected to be completed during 2018 [later delayed and not completed until 2023]. By then, 140,000 people aged 50-74 will have been offered either sigmoidoscopy once or at least one round of a total of 5 rounds [later reduced to 4 rounds] of screening for blood in the stools every two years. The article does not present any results, but refers to useful experiences, the need for quality assurance and that a school for doctors and nurses has been established to improve the quality of the endoscopy service in Norway - not just the part of the service that has to do with screening.

## 2016

20. Young GP, Senore C, Mandel JS, Allison JE, Atkin WS, Benamouzig R, Bossuyt PM, Silva M, Guittet L, Halloran SP, Haug U, Hoff G, Itzkowitz SH, Leja M<sup>14</sup>, Levin B, Meijer GA, O'Morain CA, Parry S, Rabeneck L, Rozen P, Saito H, Schoen RE, Seaman HE, Steele RJ, Sung JJ, Winawer SJ **Recommendations for a step-wise comparative approach to the evaluation of new screening tests for colorectal cancer.** *Cancer.* 2016;122:826-39, CRISTIN -16 1362467

Randomized trials on population screening against bowel cancer often require 70-100,000 participants, they are expensive (but cheaper than failed screening programs) and it is difficult to obtain funding. The time horizon is also a problem – it takes at least 10 years before one can expect

to see any reduced incidence of cancer or death due to cancer. Therefore, many national screening programs have been introduced on a poor scientific basis and more based on political good intentions and beliefs in screening. This article attempts to draw up alternatives to randomized studies where the study endpoint has traditionally been cancer death. Some new screening tests can be compared directly against known methods which have already been tested in randomized studies, but there are a number of caveats and limitations to this approach.

**Contribution to fill knowledge gap:** Increased insight into alternatives to randomized screening studies.

**Consequences and transfer value:** Useful in planning screening studies and programmes. Transfer value to screening planning.

21. *Bretthauer M, Kaminski MF, Løberg M, Zauber AG, Regula J, Kuipers EJ, Hernán MA, McFadden E, Sunde A, Kalager M, Dekker E, Lansdorp-Vogelaar I, Garborg K, Rupinski M, Spaander MC, Bugajski M, Høie O, Stefansson T, Hoff G, Adami HO. **Population-Based Colonoscopy Screening for Colorectal Cancer: A Randomized Clinical Trial.** JAMA Intern Med. 2016;176:894-902, CRISTIN -16 1364338* Many countries have introduced colonoscopy screening without prior studies that can say anything about how effective it is. This is the first randomized study comparing colonoscopy screening (31,420 people selected for screening) with no screening ("care as usual" - 63,370 people). The participants are aged 55-64 and live in Poland, Norway, the Netherlands and Sweden. This article describes variations in attendance and findings at the screening. It describes on average a very good standard of performed colonoscopies, although there is sometimes great variation between the colonoscopists when it comes to the quality of the examinations performed.  
**Contribution to fill knowledge gap:** The study provides valuable knowledge about colonoscopy screening and the quality of colonoscopies in four European countries.  
**Consequences and transfer value:** Systematic training of endoscopists and quality assurance is an international need. The study has transfer value to all screening programs for reduction of the bowel cancer burden.
22. *Berstad P, Botteri E, Larsen IK, Løberg M, Kalager M, Holme Ø, Bretthauer M, Hoff G; **Lifestyle changes at middle age and mortality: a population-based prospective cohort study.** J Epidemiol Community Health. 2016 Jun 16 CRISTIN -16 1372299*  
One may wonder sometimes if there is much point in changing to a healthier lifestyle in adulthood, or if it is just making the rest of the allotted time on Earth unnecessarily miserable. In this study, we follow 4,211 people from the age group 50-54 for an average of more than 12 years, recording lifestyle changes at the start of the study and after 3 years. The endpoint for the analyzes was death from any cause. People received a "lifestyle score" of 0-4 based on how many of the internationally recommended lifestyle tips were followed (including non-smoking, exercise, a healthy diet)  
**Contribution to fill knowledge gap:** Those who spontaneously improved their lifestyle score by one point (on a scale of 0-4) during the first 3 years of the study achieved a 38% reduced risk of death during the follow-up period.  
**Consequences and transfer value:** The study strengthens the importance of motivation and commitment to take preventive lifestyle measures even at the age of 50-60. The study has transfer value to clinical medicine.
23. *Bretthauer M, Kalager M, Adami HO, Hoff G; **Who Is for CO2? Slow Adoption of Carbon Dioxide Insufflation in Colonoscopy.** Ann Intern Med. 2016;165:145-6, CRISTIN -16 1387940*

During a colonoscopy, some gas must be blown into the intestine to be able to see the distended intestinal wall properly. In most countries, ordinary air is used for this. After the examination, remnants of this air must be released through the back passage. If a person consumes carbon dioxide, however, the gas is absorbed into the blood through the intestinal wall and disappears within a few minutes. As a result, there will also be less stomach cramping and "air" pain after the examination. Carbon dioxide also has a safety advantage because it completely removes the small risk of explosive gas formation (combined bacterial methane gas and oxygen from the air) when using air. In Norway, over 90% of colonoscopies are now performed with carbon dioxide gas, but the rest of the world is very slow to catch up. This article deals with attitudes that have prevented conversion to carbon dioxide gas.

**Contribution to fill knowledge gap:** Awareness of the benefits for patients by changing from the use of air to carbon dioxide gas during colonoscopy.

**Consequences and transfer value:** Directly transferable to routine clinics.

24. Jover R, Bretthauer M, Dekker E, Holme Ø, Kaminski MF, Løberg M, Zauber AG, Hernán MA, Lansdorp-Vogelaar I, Sunde A, McFadden E, Castells A, Regula J, Quintero E, Pellisé M, Senore C, Kalager M, Dinis-Ribeiro M, Emilsson L, Ransohoff DF, Hoff G, Adami HO; **Rationale and design of the European Polyp Surveillance (EPoS) trials**. *Endoscopy* 2016;48:571-8, CRISTIN -16 1362714  
About 20% of the colonoscopy capacity is used for checks (surveillance) after the removal of polyps. This will increase as we become better at detecting polyps, new types of polyps must be followed up and screening of healthy individuals will reveal more polyps. The benefit of spending a lot of resources on polyp control is poorly documented. This article describes the design of a large international study comparing several strategies for the control of several types of polyps. The study is coordinated from Norway with participation from centers in several European countries. The study is in the recruitment phase and results are expected to be available in 10-15 years.  
**The work's contribution to increasing knowledge:** The study presents a large international study which is underway to gain more knowledge about surveillance after removal of polyps from the large bowel.  
**Consequences and transfer value:** No transfer value to clinical work until possibly in 10-15 years.

## 2015

25. Hoff G. **Gastrointestinal cancer screening: screening may release new research funding to improve health service also in routine clinics**. *Scand J Gastroenterol* 2015 Jun;50(6):718-26. DOI: 10.3109/00365521.2015.1011225 [Link PubMed](#)  
This is an overview article of research on bowel cancer screening over the past 30 years and how this has also been of great benefit to routine clinics.  
**Contribution to fill knowledge gap:** The article refers to concrete consequences for clinical work - change from the use of air to CO<sub>2</sub> gas during colonoscopy; demonstration of a connection between smoking and precursors to cancer (polyps); studies on changes in polyps over time.  
**Consequences and transfer value:** The screening studies mentioned have led to a change in the use of insufflation gas during colonoscopy with less pain for the patients; modified guidelines to reduce surveillance after polyp removal; they have shown the need for formalized training of colonoscopists and tried out new types of colonoscopes and bowel cleansing regimes. All this has had direct transfer value to routine clinics.

26. Hoff G. *Look to Poland! Conversion from opportunistic screening to a randomized, national screening program for colorectal cancer. Endoscopy 2015 Dec;47(12):1104-5 DOI: 10.1055/s-0034-1393430 [Link PubMed](#)*

Before new treatment and other new health services (for example, screening) are introduced, we must show that this is useful, preferably through randomized studies where the new is compared against what is the prevailing standard. Often this requirement is not respected, for example when national screening programs are introduced. In Poland, a national program of colonoscopy screening (examination of the entire colon with a flexible "bowel scope") was introduced in 2000. The Polish have now realized that this should have been done with randomization of the population (drawing lots to be offered the new (screening) or current standard (no screening)) in order to gain more knowledge about the usefulness of colonoscopy screening. From 2012, the entire screening program has therefore been changed to randomization.

**Contribution to fill knowledge gap:** The Polish turnaround shows that even 12 years after initiating a screening program, it is not too late to turn it into something that can increase knowledge about screening.

**Implications and transfer value:** Transfer value to anyone running national or regional screening programs.

## 2012

27. Bretthauer M, Hoff G. *Comparative effectiveness research in cancer screening programmes. BMJ 2012;344:e2864*

National screening programs are by nature relatively static - perhaps a bit like supertankers: Once they have started, it is difficult to get them on a new course. In this article, we argue that comparative effectiveness research should be a natural part of screening programs - in line with increasing political pressure to have more research integrated into normal clinical work. As part of this line of thinking, piloting of a possible national bowel screening program was started in 2012 with a randomized trial of two current screening methods – a once-only screening round with sigmoidoscopy (examination of the lower approx. 50 cm of the bowel with a thin, flexible "bowel scope") or examination every two years testing for invisible blood in the stools. The project is carried out in Østfold County and parts of Vestre Viken with the Norwegian Cancer Registry as coordinating institution. This article briefly describes this and the importance of integrated research in all screening programmes.