

Ethical issues with colorectal cancer screening – a systematic review

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Abstract:

Rationale, aims and objectives: Colorectal cancer (CRC) screening is widely recommended and implemented. However, sometimes CRC screening is not implemented despite good evidence and some types of CRC screening are implemented despite lack of evidence. The objective of this article is to expose and elucidate relevant ethical issues in the literature on CRC screening that are important for open and transparent deliberation on CRC screening.

Methods: An axiological question based method is used for exposing and elucidating ethical issues relevant in HTA. A literature search in MEDLINE, Embase, PsycINFO, PubMed Bioethics subset, ISI Web of Knowledge, Bioethics Literature Database (BELIT), Ethics in Medicine (ETHMED), SIBIL Base dati di bioetica, LEWI Bibliographic Database on Ethics in the Sciences and Humanities and EUROETHICS identified 870 references of which 114 were found relevant according to title and abstract. The content of the included papers were subject to ethical analysis in order to highlight the ethical issues, concerns, and arguments.

Results: A wide range of important ethical issues were identified. The main benefits are reduced relative CRC mortality rate, and potentially incidence rate, but there is no evidence of reduced absolute mortality rate. Potential harms are bleeding, perforation, false test results, overdiagnosis, overtreatment (including unnecessary removal of polyps), and (rarely) death. Other important issues are related to autonomy and informed choice equal access, equity, justice, medicalization and expanding disease.

Conclusion: A series of important ethical issues have been identified and need to be addressed in open and transparent deliberation on CRC screening.

Key Words: ethics, colorectal cancer, screening, benefits, harms, autonomy, deliberation, axiology

Introduction

Colorectal cancer (CRC) is amongst the most frequently occurring malignancies and the leading cause of cancer-related death in Europe and the United States of America. CRC screening is recommended by a wide range of professional organizations, national bodies, and international communities¹⁻³. By now screening is introduced in many countries, in several countries before high quality evidence on outcomes was available. CRC screening is characterized by many available screening strategies with distinct features, advantages, and downsides making assessment (and implementation) challenging. As with all screening programs, not all individuals participating will personally benefit from participation and screening programs have the potential to harm through risks of the procedure itself, false test results, unnecessary detection and treatment, as well as anxiety or health reassurance and lowered self-care.

There are many HTAs on CRC screening, but assessment of ethical, social, and legal aspects of health promotion and disease prevention activities is often lacking⁴. A recent article presents and discusses some of the ethical issues in CRC screening⁵. This article provides an extended and a more elaborate review.

Accordingly, the aim of this article is to expose and elucidate relevant ethical issues in the literature on CRC that are important for open and transparent deliberation on CRC screening. The article does not differentiate between ethical aspects that are important for the decision on whether to implement CRC screening and aspects that are important when (not) implementing screening. The reason for this is that it may be difficult to differentiate between the aspects and because both types of aspects are important for decision makers.

CRC screening involves several stakeholders. Screening is aimed at *healthy persons* in specific age groups, normally within the age of 50-75. Relatives may become involved in the case of genetic determinants of CRC. Health professionals and industry is involved, as are health policy makers.

Moreover, several approaches are used for colorectal cancer. The most commonly used methods are colonoscopy, sigmoidoscopy, and fecal occult blood test (either guiac-based, gFOBT, or with immunological detection of humane blood, iFOBT). Hence, there are significant differences between the approaches for CRC screening (intervention).

Methods

An axiological question based (Socratic) approach for ethics in HTA was applied to identify ethical issues relevant for decision-makers⁶. A literature search was performed in order to identify relevant

ethical issues^{7,8}. The search strategy was informed by stakeholder meetings and was elaborated from a list of 33 questions of the Socratic approach and is described in detail in Appendix 1. The specific searches were performed in the following databases: MEDLINE, Embase, PsycINFO, PubMed Bioethics subset, ISI Web of Knowledge, Bioethics Literature Database (BELIT), Ethics in Medicine (ETHMED), SIBIL Base dati di bioetica, LEWI Bibliographic Database on Ethics in the Sciences and Humanities and EUROETHICS. Search strategies were elaborated for each database, due to the differences in content, indexing and search options. For the searches in MEDLINE og Embase the same search strategy for «colorectal cancer» and «screening» were applied as for a recent systematic review by Fretheim et al⁹.

All titles, abstracts, and key words of the identified references were investigated with respect to relevance to the various questions of the approach. References addressing ethical issues were examined full text, and ethical issues, concerns, considerations and arguments were included. Identified ethical issues were analyzed by a researcher trained in HTA and ethics and grouped in accordance with their content. Identified issues that were not addressed by any questions were highlighted, and questions not covered by any identified issues were scrutinized with supplementary searches in order to see if there are ethical issues that have not been identified by the literature. These supplementary efforts are based on training in ethics.

As the approach aims at comprehensiveness in covering all ethical issues, and not at exhaustiveness in identifying all references addressing the same issue, only seminal references were included for the same issue. References only mentioning that there are ethical issues without providing any substance or analysis of the issue(s) were excluded.

Results

The results from the literature search are illustrated in Figure 1.

[Figure 1 Flow chart over results from literature search]

Benefits, burdens, and harms

CRC is a type of cancer which develops relatively slow, and thus is well suited for screening. Benefits and harm will depend on uptake, skills, and organizing of screening program, i.e., on context. One such contextual evidence compilation (for Norway) is shown in Table 1. None of the methods have demonstrated a reduction in the overall mortality rate⁹. False reassurance due to screening is suggested as one reason for the discrepancy between reduction in relative and absolute mortality

rate¹⁰⁻¹² and that screening “does not actually save lives but shifts individuals to other causes of mortality” is another^{5,13}.

[Table 1 Overview of most referred benefits and harms per 1000⁹]

Benefits

The main benefits are identified as reduced CRC mortality and reduced disease incidence (for sigmoidoscopy). Table 1 shows the estimated number of deaths avoided. In addition, some may also experience reduced anxiety and health reassurance resulting from CRC screening¹⁴. Endoscopic screening also avoids some of the challenges with other screening programs, such as anxiety, because detection, diagnosis, and treatment can be delivered at the same time¹⁵.

The benefits have made several international and national organizations to recommend CRC screening, which is considered by many to be an ethical imperative¹⁶.

Harms

As seen in Table 1, bleeding, perforation, and death are potential harms resulting from (subsequent) endoscopic procedures. Severe bleeding resulting from (subsequent) colonoscopy is observed in 0-0.2% of cases¹⁷. The risk of death is estimated to be 0.002 % for colonoscopy⁹.

Other identified harms are false test results (negative and positive), overdiagnosis, overtreatment, and adverse effects of such diagnostics and treatment. False positive test results generate a risk of people having to undergo unnecessary diagnostic tests and may generate worries of having a disease that is not present¹⁸ and can result in reduced adherence¹⁹. False-negative test-results can give rise to false reassurance and thereby possible ignorance of future symptoms of cancer, ultimately resulting in delayed diagnosis²⁰ and poorer outcomes.

Overdiagnosis is rarely assessed. Only one study has assessed overdiagnosis for early detection in CRC screening, and estimated an overdiagnosis rate of 0.1-0.9%²¹. The reason for this may be that the main focus has been prevention and not early detection and the definition of overdiagnosis. By only including manifest CRC in the definition of overdiagnosis, the numbers will be small. However, if one would include all polyps acted upon (which would not evolve to manifest CRC) the overdiagnosis rates would be much higher.

Prevention CRC screening aims at identifying and removing precursors of disease. However most resected colonic polyps would not have otherwise caused morbidity or death as they would not advance to disease and many of them would regress²². Identification and removal of such lesions represents overdiagnosis and overtreatment, respectively, and the overdiagnosis (“overreporting,”

“oversurveillance”) and overtreatment rate is substantial as most of the identified lesions would not have developed to CRC if they were not detected, and the trend is to find ever smaller lesions²³. However, polypectomy is considered to be far less invasive and cumbersome than the treatment of cancer, and therefore considered to be less morally challenging⁵. Nonetheless, it has been pointed out that CRC screening can inflict psychological distress on persons screened and be a source of large costs and resources⁵. However, no calculations of such costs have been identified. The detection and removal rate of non-advanced adenomas is strongly increasing²³. While this is done to decrease the number of interval cancers and the CRC mortality rate, it comes at the cost of a substantial increase in unnecessary detection and removal of adenomas. Hence, overuse as well as underuse have been identified²⁴ as moral problems, and it has been argued that improved survival is associated with improvement in treatment as much as with early detection²⁵.

The main burdens are related to (endoscopic) examinations. Moderate or severe abdominal pain after colonoscopy are reported to be common for persons examined with standard air insufflation (16.6%) and less so with carbon dioxide (CO₂) insufflation (4%)¹⁷.

There has also been a worry about CRC screening having a negative effect on lifestyle in general^{11,26,27}, due to health reassurance. On the other hand it has been pointed out that information about CRC and screening can cause anxiety²⁸, and anxiety with test results is reported²⁹.

Benefits versus harms

Benefits and harms are core factors for a utilitarian analysis together with costs. Costs will vary from country to country. A recent Norwegian cost-effectiveness analysis of CRC screening at the age of 55 shows that the incremental cost-effectiveness ratio (ICER) was estimated to be 12 930 USD/QALY for sigmoidoscopy for men and 17 443 USD/QALY for women in a health services perspective. For iFOBT and colonoscopy the numbers are based on additional assumptions as high quality study results are not ready yet. For iFOBT the ICER is estimated to be 31 224 USD/QALY for men and 23 799 USD/QALY for women (biannually, 10 rounds). For colonoscopy the ICER is estimated to be 18 097 USD/QALY for men and 24 077 USD/QALY for women³⁰.

Balancing benefits and harms is identified as one of the major ethical challenges with screening in general and CRC screening in particular³¹. One reason may be that lead time and length time bias may make assessment of benefits and risks demanding⁵. Another is that harm and risk may vary with comorbidity and medication (e.g., blood thinners). Moreover, persons may balance benefits and burdens differently, e.g., health care professionals and patients may value true positives and false positives differently³².

Assessing outcomes for various screening strategies is also difficult due to complexity³³, e.g., using a non-invasive initial screening test (gFOBT or iFOBT) may increase uptake but increase anxiety and decrease efficiency. The same goes for the apparently technical question of setting cut-off values³⁴. All these issues make it a complex matter balancing benefits and harms.

Uptake

Uptake varies greatly with screening method³⁵ with gender³⁶, ethnic group^{37,38}, religiosity³⁹, distance to facility⁴⁰, and country. Uptake varies between 58% to 90% in high quality studies on outcome⁹. There is considerable variation in CRC screening by sociodemographic characteristics^{34,41}, by information provided^{42,43}, by the provider's understanding of patient's social context⁴⁴, but also due to different world view, e.g. fatalism (the view that all events are subject to fate or are inevitable)⁴⁵. Moreover, high risk groups may have lower participation rates⁴⁶⁻⁴⁸. All such circumstances may result in selection bias in outcome studies.

Maintaining participation throughout successive screening invitations is identified as a core challenge^{34,49}. Uptake extensively depends on trust, which is a cherished but delicate value in health care.

Uptake is also related to questions of autonomy and consent. Historically, beneficence has trumped autonomy in order to increase the uptake, and hence the outcome of a screening program. Even today it is acknowledged that increasing uptake, and hence population health, is a multifaceted and difficult task⁵⁰.

Autonomy, information, and consent

Respecting people's autonomy and obtaining real expressed informed consent are identified as some of the major ethical challenges with CRC screening^{31,51}. In this informing about risks and benefits in a balanced manner is challenging⁵². Studies also show that adults want full information on risks and benefits of screening while they also want a recommendation from an authoritative source⁵³. Emotional aspects and friends' subjective norms tend also to be very important for decisions to participate and to adherence⁵⁴. Factors other than provision of information appear to determine people's CRC screening preferences^{46,55}, especially for elderly^{56,57}.

The very different characteristics of the various screening tests prompt the question of whether invitees should be able to choose which screening method they find most appropriate according to their preferences^{58,59}. Choice of CRC screening method varies. One large study found that patients who were offered an informed choice for screening had higher adherence rates than patients who were not offered a choice of screening test⁶⁰. On the other hand, a minority of persons being screened report to have been asked about their preferences⁶¹, and preferences tend to vary⁶².

Knowledge of CRC screening is also very variable⁶³ and a great number of invited persons do not make informed decisions about screening⁶⁴. Information may overstate benefits⁶⁵ probably to increase uptake⁵. Accordingly, the quality of informed consent has been demonstrated to be low⁶⁶. Nonetheless, people tend to want to be informed about risks⁶⁷.

Informed decision-making may reduce the participation in screening^{68,69}. Therefore nudging and biased information has been suggested for CRC surveillance⁷⁰, and also for screening⁷¹. Ways to try to counterbalance “optimistic bias” have also been suggested (see below)⁷². However, nudging and biased information is controversial as it breaches with standard conceptions of the principle of autonomy. Correspondingly, incentives may increase uptake of CRC screening⁷³, but has been rejected on moral grounds⁷⁴.

Providing balanced information has been identified as a substantial challenge^{75,76}. One of the reasons for the challenges with informing about CRC screening is the (previously mentioned) complexity, and because it is hard to relate populational data to individuals and because of what has been called the ‘prevention paradox,’ i.e., that although the screening will be of significant benefit to the population as a whole, the individual’s decision to get screened regularly may only have a small impact on that individual’s risk of disease in the near future⁷⁷. Even personalized quantitative colorectal cancer (CRC) risk information is shown to have different effects on individuals⁷⁸, making personal targeting difficult. Moreover, enthusiasm has spurred biased information⁷⁹.

Accordingly, there may be many barriers to making informed choice, both personal (for potential participants)⁵⁷ and professional⁸⁰. Crucial information is not always available, such as on overdiagnosis (early detection), number of polyps detected and removed without benefit (overdetection and overtreatment with preventive screening). Moreover, for screening programs with initial non-invasive screening tests information about subsequent invasive tests may reduce uptake, posing an ethical dilemma⁸¹. Another challenge is that people typically believe their health risks are lower than those of others (i.e., optimistic bias)⁸². Yet another psychological effect is defensive information processing about colorectal cancer screening⁸³.

A wide range of measures to improve information to participants and increase informed consent have been suggested and tested^{65,72,84-91}. These may cause dilemmas of their own, for example, targeting information to African Americans implies the risk of making people aware of disparities and disadvantages⁹². Lack of awareness and misconceptions are identified as reasons for lack of outcome from actions against CRC⁹³. As information may result in anxiety²⁸ or “cancer information overload”, this poses a moral dilemma. However, ways of informing may reduce the risk of anxiety and overload, and contextual sensitivity appears to be important⁹⁴. On the other hand, some persons

view participation as accepting an offer, where being informed does not impact on participation rates⁵¹. Moreover, different groups may have very different needs for information^{95,96} and it can be difficult to predict their information preferences⁹⁷.

Hence, providing relevant information may be challenging and resource demanding⁹⁸. Knowledge about the efficiency of the various methods for promoting informed consent is limited and no one method appears to stand out in efficiency^{84,99}.

Practical challenges with screening - ethical implications

Due to the many options, optimizing screening strategies is identified as a chief challenge³⁴. Tailoring the frequency of screening and limiting intervention for polyps that are not believed to be precursors to morbid disease, have been key practical challenges with moral connotations²². So is providing risk based personalized screening¹⁰⁰.

How to assess and balance the various CRC screening strategies is demanding. Evidence for gFOBT and sigmoidoscopy is available, while we still have to wait many years for high quality results from comparative studies with iFOBT and colonoscopy⁹. Whether one should introduce CRC screening programs with one or more of the tests where high quality evidence is available, or whether to introduce alternative promising screening strategies based on preliminary evidence (and modelling), or whether to set up screening programs as (long lasting and costly) scientific studies poses significant moral quandary. In the latter case, also which design to use and which screening tests to include. Moreover, offering gFOBT as one of the arms in a study could breach the criteria for equipoise (in research ethics).

Other practical issues, such as specific staffing, financial, and training¹⁰¹ may also have moral implications¹⁰² as well as unreachable referred patients and medical ineligibility (e.g., symptomatic comorbid conditions)¹⁰³ as target group may not be reached as intended. Such complexities of screening programs as well as a range of organizational challenges have been discussed¹⁰⁴⁻¹⁰⁸, e.g., how to coordinate screening centers with ordinary clinical activities, and ignoring such challenges may result in suboptimal implementation.

Moreover, timing of implementation is a major concern, as CRC screening programs are resource demanding and take time to roll out. As some methods are easier to implement than others, they could provide screening to greater parts of the population faster. Implementing what is presently considered to be the best screening test may exclude many from being screened (due to timing issues) and the test may turn out to be inferior when the program is fully implemented.

How to communicate screening results in a gentle, correct, and comprehensive manner is also a challenge¹⁰⁹. Yet another issue that follows from implementing screening is what to do with regards to assessing the risk of family members of persons identified with CRC by screening. Some clinicians have pointed out that this represents a pertinent moral dilemma, as they think that all family members of persons with CRC should be screened, while they do not take the time to do so¹¹⁰. On the other hand contacting family members conflict with the right to privacy and the right not to know.

Due to a potential "health certificate effect" in CRC screening (where a test functions as a certificate of being healthy and having a negative effects on health awareness and lifestyle changes) there may be a need for extensive participant education^{10,11}. Moreover, tailored advice given in the context of cancer screening may provide an opportunity to improve dietary behaviors¹¹¹.

Equity and Equal Access

Due to geographical variations between and within several countries, the access to screening (and uptake) may vary, and disparities in CRC screening have been identified¹¹²⁻¹¹⁹. For example, a strong inter-physician variation and inter-center variation in the adenoma detection rate (ADR) has been demonstrated, even after adjustment for patient factors²³. Discrepancies in lifestyle have been illustrated, where people being more physically active were more likely to participate¹²⁰. Disparities with respect to race/ethnicity are identified¹²¹⁻¹²⁴. Persons with mobility disabilities are less likely to access cancer screening¹²⁵. Reduced health literacy may also generate differences in uptake¹²⁶⁻¹²⁸ and access to screening, e.g., web sites providing information may be too difficult for the average (American) adult and much too difficult for adults with limited literacy¹²⁹ or cognitive capacity¹³⁰. While making an informed decision about participation in colorectal cancer (CRC) screening may be challenging for invitees with lower health literacy skills, the association between health literacy and informed decision making is complex¹³¹. Some groups have also shown higher rates of false test results¹³².

Hence, reaching the underserved remains a core challenge³⁴. Various measures to reach underserved groups have been suggested⁴⁹, but some may conflict with ethical principles, such as respect for autonomy.

Additionally, adherence to screening guidelines is varying¹³³⁻¹³⁵, probably also due to more or less reflected professional disagreement or perspectives^{41,136,137}. Cost-effectiveness information appears to have little influence on physicians' cancer screening recommendations¹³⁸.

Accordingly, equity and equal access are important moral issues. So is the question of how to balance equity and efficiency. Some studies show that equity trumps efficiency¹³⁹, i.e., that equal access to screening with respect to gender and age is considered to be more important than to select those groups where screening is most efficient (independent of gender and age).

Justice

Studies show less effect of CRC screening with women^{140,141}. This raises the question of how to provide just screening programs for men and women. The same challenge exists for age, as the number of polyps increase significantly at the age 55-70 while CRC incidence increases at age 65-70. This makes it challenging to set lower and upper age limit^{142,143}. At the same time, screening risks may increase for older persons^{144,145}, while the capacity to adhere to test preparations may decrease¹⁴⁶ and to consent may decrease in older persons. However, whether age is a selection criterion is contested^{147,148}.

Various groups may also differ significantly in risk^{100,149}, and there are differences in how various groups experience burdens of endoscopy. “Mathematically just” may appear “emotionally unjust” in the population. Hence, which group to offer screening (and where to set limits, e.g. to age and cut-offs) poses significant ethical challenges which are important for decision makers and health policy makers implementing screening programs. On the other hand, CRC does not have a social gradient and is not suitable for evening the playing field¹⁵⁰, i.e., to reduce the differences in health.

If screening programs drain resources from cancer surveillance and treatment it may pose ethical challenges (with respect to priority setting). This is especially problematic for high rates of overdiagnosis and overuse. Another identified issue is that insurance companies may restrict insurance or increase insurance premium, as a positive test result may indicate an increased risk of disease,¹⁵¹

At a more general level, whether it is right to use resources on health services for many healthy people for a condition that only relevant for a small fraction of the population (4%)^{24,150}, where there is a significant delay before results are experienced (10-15 years)¹⁵², and where there is no overall reduction of mortality, while relevant alternatives exist¹⁵³ is a key moral question.

The ethics of evidence and action

Evidence does not dictate implementation. Despite evidence and recommendations, several countries have not implemented screening¹⁵⁴⁻¹⁵⁶. On the other hand, some types of screening have been implemented without high quality evidence, e.g., with iFOBT and colonoscopy. Although such

decisions may be based on accuracy data and modelling studies, making it “unethical not to screen,” it can become difficult to obtain evidence on these screening strategies in the future⁵.

Altering conceptions of disease

One important question that was not addressed in the literature is the status and prestige of the disease and the means to prevent, detect, and treat it. CRC is organ specific and can be detected with advanced technology. Accordingly, it has a high prestige to physicians¹⁵⁷. Cancer also has a special position amongst diseases¹⁵⁸. Screening changes the attention on and the conception of a disease. It also alters the end of health care services, from avoiding death due to CRC to avoid development of tumors¹⁵⁹. Therefore, screening against CRC may well increase its status.

Polyps are very frequent in the (elderly) population, and they normally do not result in symptoms, disease, or death. With screening they become target of medical attention and treatment, i.e., making them disease (proto-disease, pseudodisease). Previously serrated lesion of the colorectum were not considered to be significant, but are now considered to be pre-cancers (preconditions for cancers)^{160,161}. Making polyps subject to medical attention has been criticized for being a kind of medicalization¹⁶². Invitation to screening may also result in worries and in people seeing themselves as patients¹⁶³, i.e., changing their self-conception and contributing to the medicalization of ordinary phenomena. Also, as people who remove polyps/adenomas are followed up they become patients (every 1, 3, or 10 years).

Moreover, removal of premalignant conditions may be conceived of as a form of human enhancement and promote an ideal image of a human being. This may pave the way for other types of enhancements: “we improve human beings by removing (normal) polyps (X), so why should we not improve human beings by doing Y?” This mode of reasoning is frequently referred to as “the slippery slope argument” and is somewhat controversial^{164,165}.

Having and removing polyps may also change persons’ self-conception, e.g., their vulnerability on the one hand and their improved health status on the other (“the health certificate effect”). Moreover, a safety net of screening may also make people expose themselves to risks, i.e., “moral hazard.”¹².

Hence, screening programs and conceptions of cancer may change conceptions of self and alter our ways of communicating¹¹⁹.

A rose by any other name?

As CRC screening focuses on polyps, it appears to be important what the screening program is called. Calling it a “colorectal cancer screening program” only covers the detection part of screening, and would be misleading. Calling it a cancer prevention screening program may be more formally correct,

but people would probably think that it detects cancers early. Calling it a “polyp resection program” would be more correct, but would probably not promote a high uptake. Hence, the name is more than a formality, as the choice will determine the measures for the benefits and the harms. A polyp resection program may have zero (cancer) overdiagnosis, as (almost) no cancer diagnosis is made. Polyps are detected and resected. However, a CRC screening program may have significant overdiagnosis, contrary to what it is considered to be today ²¹.

Some legal aspects

It has been pointed out in the literature that introducing screening legislation has been shown not to have any clear impact on disease incidence (in terms of reduction) ¹⁶⁶, and that CRC screening touches on legal provisions regarding confidentiality of patients and other human rights issues ¹⁵¹.

Cut-offs and Incidental findings

One of the identified challenges is to decide on cut-off values ^{34,167}, e.g., for polyp size. Removing very low risk polyps at a small but real risk may be morally challenging.

A related problem is return of incidental findings. Several of the methods may find other health-related problems, and how to handle these may result in moral dilemmas.

Discussion

This review has identified a wide range of ethical issues. Some are related to basic ethical principles, such as autonomy, beneficence, nonmaleficence, and justice while others connect to basic concepts for health care, such as disease. Yet others connect to societal aspects, such as medicalization and overtreatment.

It is difficult to stop screening when you have started, and disinvestments are hard to make ^{168,169}. Hence, thorough assessment appears to be warranted. It may be possible to state specific aims, and if these aims are not achieved in a given time frame, the program will be terminated.

Although some ethical issues are extensively discussed in the literature, such as informed consent, it does not necessarily mean that informed consent is a particularly challenging issue with CRC screening, as the many references may stem from the fact that informed consent has obtained much attention in general.

A wide range of relevant related issues have not been addressed in this review, e.g., issues specific to emerging (biomarker or imaging) tests for CRC and the relationship between CRC and other (genetic)

diseases, such as Lynch syndrome. Although such issues obviously raise a series of ethically relevant questions, they are beyond the scope of this review.

Some issues appear rather technical, e.g., whether to assess and inform about screening programs based on relative or absolute CRC risk reduction^{170,171}. However, such questions have strong moral bearings, which it is important to acknowledge in order to facilitate an open and transparent deliberation. Informing the public that CRC screening reduces mortality (in general) may be misleading⁷⁹.

Most of the identified ethical issues are covered by the questions of the axiological method⁶, but not all, e.g., some of the practical challenges are not explicitly included in the questions. Moreover, several of the questions address issues not found in the literature, e.g., whether it affects religious convictions, and whether screening would increase the status and prestige of the disease. Other methods for addressing ethical issues¹⁷² could of course have been applied. However, this review has identified a series of other ethical issues than previous studies⁵ and is in line with other studies on ethics in screening^{31,173}.

From exposing and elucidating the relevant ethical issues one would ask for specific recommendations. Should we implement CRC screening, or not? If yes, what kind of screening program? As these questions have to be answered in context, this review only provides input for the contextual decision-making process. In the same manner as evidence does not dictate implementation¹⁵⁴⁻¹⁵⁶, neither does a review of the ethical issues, i.e., there is *no ethical "imperative of evidence."* Nonetheless, the review can prepare and facilitate this process.

Conclusion

This review has identified a wide range of important ethical issues. First and foremost, it has revealed how complex CRC screening is and how difficult this makes a utilitarian analysis of benefits and harms. While predictive CRC screening poses problems with false test results and overdiagnosis, preventive screening proffers problems with overdiagnosis and overtreatment. All screening presents potential harms due to the procedures, such as bleeding, perforation, and (seldom) death. These issues have to be balanced against the benefits of screening, such as reduced relative mortality and incidence rate.

Moreover, the question of participants' choice (autonomy) emerges as important. So do challenges with informing about screening in a manner that promotes and assures informed choice and at the same time reinforces uptake. Assuring equal access, equity in uptake, and justice surface as

important ethical issues, e.g., in the question of which groups should be offered which screening (age, gender, risk class). Reaching the underserved is a core issue.

Societal issues, such as medicalization of ordinary conditions, changing the conception of disease, medicalization, and paving the way for enhancement, are also relevant.

In utilitarian terms the crucial moral question is whether it is right to perform 5700 colonoscopies, of which 11 will have their colon perforated, 914 will have moderate or severe abdominal pain, 2860 will have polyps removed unnecessarily, and 0-1 will die, in order to prevent 157 to die from CRC for every 100000 persons invited, without reducing the overall mortality rate.

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Figure 1 Results from literature search

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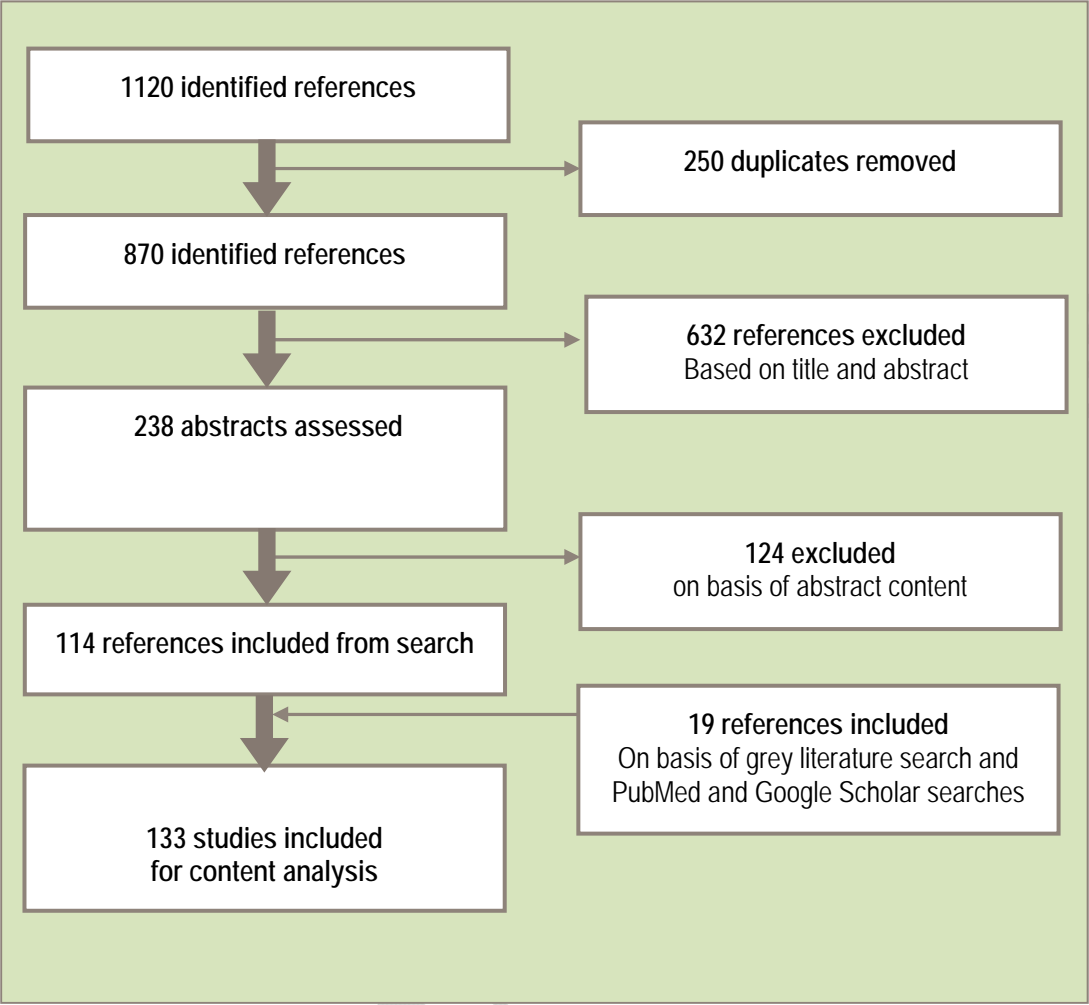


Figure 1 Results from literature search

Table 1 Overview of most referred benefits and harms per 1000⁹

Screening Method	Reduced # CRC deaths per 1000	Direct Complications	False positives	Complications from subsequent testing	Unnecessary removal of polyps and follow up	Missed cancers
gFOBT (cut off 75 µg/L buffer)	3 From 26 to 23 (14%)	None	12 (1.2%)	0.3 (0.03%) Bleeding, perforation, death, colonoscopy	?	5 (0.5%)
iFOBT (FIT)	?	None	90 (9%) at 70-75 mg/ml	? Bleeding, perforation, death, colonoscopy	?	0.2 (0.02%) at 70-75 mg/ml
Sigmoido- scopy	7 From 26 to 19 (27%)	1 0,08 %	?	2 per 1000 perforations with subsequent colonoscopy	290	?
Colonoscopy	No results from RCTs yet	0.1 perforation 2 major bleedings 4.2 vasovagal reactions 166 abdominal pain	?	NA	481	?

? signifies that no high quality evidence is available