

ORIGINAL ARTICLE

# 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 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.

## KEYWORDS

autonomy, axiology, benefits, colorectal cancer, deliberation, ethics, harms, screening

## 1 | INTRODUCTION

Colorectal cancer (CRC) is among the most frequently occurring malignant tumors and the leading cause of cancer-related death in Europe and the United States of America. The CRC screening is recommended by a wide range of professional organizations, national bodies, and international communities.<sup>1–3</sup> By now screening is introduced in many countries, in several countries before high-quality evidence on outcomes was available. The 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 lacking.<sup>4</sup> A recent article presents and discusses some of the ethical issues in CRC screening.<sup>5</sup> 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.

The CRC screening involves several stakeholders. Screening is aimed at *healthy persons* in specific age groups, normally within the age of 50 to 75 years. 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 CRC. 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).

## 2 | METHODS

An axiological question-based (Socratic) approach for ethics in HTA was applied to identify ethical issues relevant for decision makers.<sup>6</sup> A literature search was performed to identify relevant ethical issues.<sup>7,8</sup> 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, because of the differences in content, indexing, and search options. For the searches in MEDLINE and Embase the same search strategy for «colorectal cancer» and «screening» were applied as for a recent systematic review by Fretheim et al.<sup>9</sup>

All titles, abstracts, and keywords 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 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.

## 3 | RESULTS

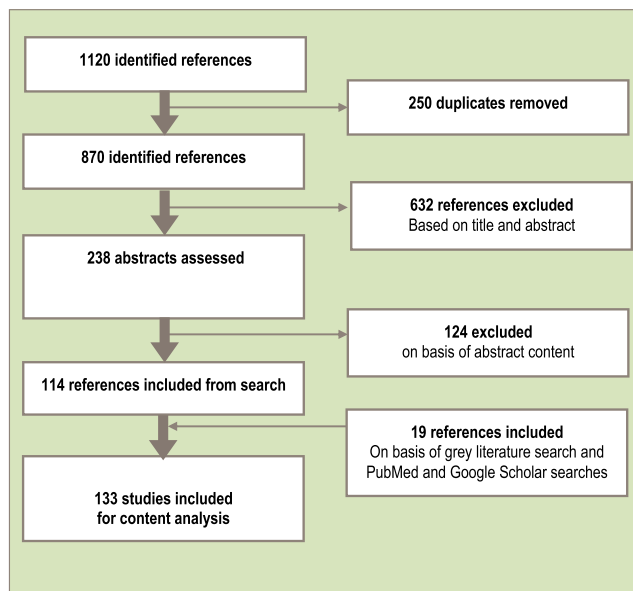


FIGURE 1 Flowchart over results from literature search

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### 3.1 | Benefits, burdens, and harms

The CRC is a type of cancer that develops relatively slow and thus is well suited for screening. Benefits and harm will depend on uptake, skills, and organizing of screening program, ie, on context. One such contextual evidence compilation (for Norway) is shown in Table 1. None of the methods has demonstrated a reduction in the overall mortality rate.<sup>9</sup> False reassurance due to screening is suggested as one reason for the discrepancy between reduction in relative and absolute mortality rate<sup>10–12</sup> and that screening “does not actually save lives but shifts individuals to other causes of mortality” is another.<sup>5,13</sup>

### 3.2 | 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 screening.<sup>14</sup> 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 time.<sup>15</sup>

The benefits have made several international and national organizations to recommend CRC screening, which is considered by many to be an ethical imperative.<sup>16</sup>

### 3.3 | 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% to 0.2% of patients.<sup>17</sup> The risk of death is estimated to be 0.002 % for colonoscopy.<sup>9</sup>

Other identified harms are false test results (negative and positive), overdiagnosis, overdiagnosis, overtreatment, and adverse effects of such diagnostics and treatment. False positive test results generate a risk of people having to undergo unnecessary diagnostic



**TABLE 1** Overview of most referred benefits and harms per 1000<sup>a</sup>

| 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<br>From 26 to 23 (14%)      | None  | 12<br>(1.2%)              | 0.3 (0.03%) Bleeding, perforation, death, colonoscopy | ?   | 5 (0.5%)                      |
| iFOBT (FIT)                    | ?                             | None  | 90<br>(9%) at 70-75 mg/mL | ?<br>Bleeding, perforation, death, colonoscopy        | ?   | 0.2 (0.02%)<br>at 70-75 mg/mL |
| Sigmoido-scopy                 | 7<br>From 26 to 19 (27%)      | 1<br>(0.08%)  | ?                         | 2 per 1000 perforations with subsequent colonoscopy   | 290   | ?                             |
| Colonoscopy                    | No results from RCTs yet      | 0.1 perforation<br>2 major bleedings<br>4.2 vasovagal reactions<br>166 abdominal pain | ?                         | NA  | 481   | ?                             |

Question mark (?) signifies that no high-quality evidence is available

tests and may generate worries of having a disease that is not present<sup>18</sup> and can result in reduced adherence.<sup>19</sup> False-negative test results can give rise to false reassurance and thereby possible ignorance of future symptoms of cancer, ultimately resulting in delayed diagnosis<sup>20</sup> and poorer outcomes.

Overdiagnosis is rarely assessed. Only 1 study has assessed overdiagnosis for early detection in CRC screening and estimated an overdiagnosis rate of 0.1% to 0.9%.<sup>21</sup> 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 on (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 regress.<sup>22</sup> Identification and removal of such lesions represents overdetection and overtreatment, respectively, and the overdetection (“overreporting” and “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 lesions.<sup>23</sup> However, polypectomy is considered to be far less invasive and cumbersome than the treatment of cancer and therefore considered to be less morally challenging.<sup>5</sup> Nonetheless, it has been pointed out that CRC screening can inflict psychological distress on persons screened and be a source of large costs and resources.<sup>5</sup> However, no calculations of such costs have been identified. The detection and removal rate of nonadvanced adenomas is strongly increasing.<sup>23</sup> 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 and underuse have been identified<sup>24</sup> as moral problems, and it has been argued that improved survival is associated with improvement in treatment as much as with early detection.<sup>25</sup>

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%).<sup>17</sup>

There has also been a worry about CRC screening having a negative effect on lifestyle in general,<sup>11,26,27</sup> because of health reassurance. On the other hand, it has been pointed out that information about CRC and screening can cause anxiety,<sup>28</sup> and anxiety with test results is reported.<sup>29</sup>

### 3.4 | 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 women.<sup>30</sup>

Balancing benefits and harms is identified as one of the major ethical challenges with screening in general and CRC screening in particular.<sup>31</sup> One reason may be that lead time and length time bias may make assessment of benefits and risks demanding.<sup>5</sup> Another is that harm and risk may vary with comorbidity and medication (eg, blood thinners). Moreover, persons may balance benefits and burdens differently, eg, health care professionals and patients may value true positives and false positives differently.<sup>32</sup>

Assessing outcomes for various screening strategies is also difficult because of complexity,<sup>33</sup> eg, using a noninvasive 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 values.<sup>34</sup> All these issues make it a complex matter balancing benefits and harms.

### 3.5 | Uptake

Uptake varies greatly with screening method<sup>35</sup> with sex,<sup>36</sup> ethnic group,<sup>37,38</sup> religiosity,<sup>39</sup> distance to facility,<sup>40</sup> and country. Uptake varies from 58% to 90% in high-quality studies on outcome.<sup>9</sup> There is considerable variation in CRC screening by sociodemographic characteristics,<sup>34,41</sup> by information provided,<sup>42,43</sup> by the provider's understanding of patient's social context,<sup>44</sup> and also by different world view, eg, fatalism (the view that all events are subject to fate or are inevitable).<sup>45</sup> Moreover, high-risk groups may have lower participation rates.<sup>46-48</sup> All such circumstances may result in selection bias in outcome studies.

Maintaining participation throughout successive screening invitations is identified as a core challenge.<sup>34,49</sup> 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 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 task.<sup>50</sup>

### 3.6 | 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.<sup>31,51</sup> In this information about risks and benefits in a balanced manner is challenging.<sup>52</sup> Studies also show that adults want full information on risks and benefits of screening while they also want a recommendation from an authoritative source.<sup>53</sup> Emotional aspects and friends' subjective norms tend also to be very important for decisions to participate and to adherence.<sup>54</sup> Factors other than provision of information appear to determine people's CRC screening preferences,<sup>46,55</sup> especially for older people.<sup>56,57</sup>

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.<sup>58,59</sup> 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 test.<sup>60</sup> On the other hand, a minority of persons being screened report to have been asked about their preferences,<sup>61</sup> and preferences tend to vary.<sup>62</sup>

Knowledge of CRC screening is also very variable,<sup>63</sup> and a great number of invited persons do not make informed decisions about screening.<sup>64</sup> Information may overstate benefits<sup>65</sup> probably to increase uptake.<sup>5</sup> Accordingly, the quality of informed consent has been demonstrated to be low.<sup>66</sup> Nonetheless, people tend to want to be informed about risks.<sup>67</sup>

Informed decision making may reduce the participation in screening.<sup>68,69</sup> Therefore, nudging and biased information has been suggested for CRC surveillance,<sup>70</sup> and also for screening.<sup>71</sup> Ways to try to counterbalance "optimistic bias" have also been suggested (see below).<sup>72</sup> 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 screening,<sup>73</sup> but has been rejected on moral grounds.<sup>74</sup>

Providing balanced information has been identified as a substantial challenge.<sup>75,76</sup> 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," ie, 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 future.<sup>77</sup> Even personalized quantitative CRC risk information is shown to have different effects on individuals,<sup>78</sup> making personal targeting difficult. Moreover, enthusiasm has spurred biased information.<sup>79</sup>

Accordingly, there may be many barriers to making informed choice, both personal (for potential participants)<sup>57</sup> and professional.<sup>80</sup> Crucial information is not always available, such as on overdiagnosis (early detection) and number of polyps detected and removed without benefit (overdetection and overtreatment with preventive screening). Moreover, for screening programs with initial noninvasive screening tests information about subsequent invasive tests may reduce uptake, posing an ethical dilemma.<sup>81</sup> Another challenge is that people typically believe their health risks are lower than those of others (ie, optimistic bias).<sup>82</sup> Yet another psychological effect is defensive information processing about CRC screening.<sup>83</sup>

A wide range of measures to improve information to participants and increase informed consent have been suggested and tested.<sup>65,72,84-91</sup> These may cause dilemmas of their own, for example, targeting information to African Americans implies the risk of making people aware of disparities and disadvantages.<sup>92</sup> Lack of awareness and misconceptions are identified as reasons for lack of outcome from actions against CRC.<sup>93</sup> As information may result in anxiety<sup>28</sup> 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 important.<sup>94</sup> On the other hand, some persons view participation as accepting an offer, where being informed does not impact on participation rates.<sup>51</sup> Moreover, different

groups may have very different needs for information,<sup>95,96</sup> and it can be difficult to predict their information preferences.<sup>97</sup>

Hence, providing relevant information may be challenging and resource demanding.<sup>98</sup> Knowledge about the efficiency of the various methods for promoting informed consent is limited, and no one method appears to stand out in efficiency.<sup>84,99</sup>

### 3.7 | Practical challenges with screening—ethical implications

Due to the many options, optimizing screening strategies is identified as a chief challenge.<sup>34</sup> 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 connotations.<sup>22</sup> So is providing risk-based personalized screening.<sup>100</sup>

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 colonoscopy.<sup>9</sup> 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 on the basis of preliminary evidence (and modeling), 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 training<sup>101</sup> may also have moral implications<sup>102</sup> as well as unreachable referred patients and medical ineligibility (eg, symptomatic comorbid conditions)<sup>103</sup> as target group may not be reached as intended. Such complexities of screening programs and a range of organizational challenges have been discussed,<sup>104–108</sup> eg, 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 (because of 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 challenge.<sup>109</sup> Yet another issue that follows from implementing screening is what to do regarding 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 so.<sup>110</sup> 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.<sup>10,11</sup> Moreover, tailored advice given in the context of cancer screening may provide an opportunity to improve dietary behaviors.<sup>111</sup>

### 3.8 | 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 identified.<sup>112–119</sup> For example, a strong interphysician variation and intercenter variation in the adenoma detection rate has been demonstrated, even after adjustment for patient factors.<sup>23</sup> Discrepancies in lifestyle have been illustrated, where people being more physically active were more likely to participate.<sup>120</sup> Disparities with respect to race/ethnicity are identified.<sup>121–124</sup> Persons with mobility disabilities are less likely to access cancer screening.<sup>125</sup> Reduced health literacy may also generate differences in uptake<sup>126–128</sup> and access to screening, eg, web sites providing information may be too difficult for the average (American) adult and much too difficult for adults with limited literacy<sup>129</sup> or cognitive capacity.<sup>130</sup> While making an informed decision about participation in CRC screening may be challenging for invitees with lower health literacy skills, the association between health literacy and informed decision making is complex.<sup>131</sup> Some groups have also shown higher rates of false test results.<sup>132</sup>

Hence, reaching the underserved remains a core challenge.<sup>34</sup> Various measures to reach underserved groups have been suggested,<sup>49</sup> but some may conflict with ethical principles, such as respect for autonomy.

Additionally, adherence to screening guidelines is varying,<sup>133–135</sup> probably also because of more or less reflected professional disagreement or perspectives.<sup>41,136,137</sup> Cost-effectiveness information appears to have little influence on physicians' cancer screening recommendations.<sup>138</sup>

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 efficiency,<sup>139</sup> ie, that equal access to screening with respect to sex and age is considered to be more important than to select those groups where screening is most efficient (independent of sex and age).

### 3.9 | Justice

Studies show less effect of CRC screening with women.<sup>140,141</sup> 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 to 70 while CRC incidence increases at age 65 to 70. This makes it challenging to set lower and upper age limit.<sup>142,143</sup> At the same time, screening risks may increase for older persons,<sup>144,145</sup> while the capacity to adhere to test preparations may decrease<sup>146</sup> and to consent may decrease in older persons. However, whether age is a selection criterion is contested.<sup>147,148</sup>

Various groups may also differ significantly in risk,<sup>100,149</sup> 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, eg, 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 field,<sup>150</sup> ie, 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 overdetection 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.<sup>151</sup>

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%),<sup>24,150</sup> where there is a significant delay before results are experienced (10-15 years),<sup>152</sup> and where there is no overall reduction of mortality, while relevant alternatives exist<sup>153</sup> is a key moral question.

### 3.10 | The ethics of evidence and action

Evidence does not dictate implementation. Despite evidence and recommendations, several countries have not implemented screening.<sup>154-156</sup> On the other hand, some types of screening have been implemented without high-quality evidence, eg, with iFOBT and colonoscopy. Although such decisions may be based on accuracy data and modeling studies, making it “unethical not to screen,” it can become difficult to obtain evidence on these screening strategies in the future.<sup>5</sup>

### 3.11 | 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. The CRC is organ specific and can be detected with advanced technology. Accordingly, it has a high prestige to physicians.<sup>157</sup> Cancer also has a special position among diseases.<sup>158</sup> Screening changes the attention on and the conception of a disease. It also alters the end of health care services, from avoiding death because of CRC to avoid development of tumors.<sup>159</sup> Therefore, screening against CRC may well increase its status.

Polyps are very frequent in the (older people) population, and they normally do not result in symptoms, disease, or death. With screening they become target of medical attention and treatment, ie, making them disease (protodisease and psudodisease). Previously serrated lesion of the colorectum were not considered to be significant, but are now considered to be precancers (preconditions for cancers).<sup>160,161</sup> Making polyps subject to medical attention has been criticized for being a kind of medicalization.<sup>162</sup> Invitation to screening may also result in worries and in people seeing themselves as patients,<sup>163</sup> ie, 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.<sup>164,165</sup>

Having and removing polyps may also change persons' self-conception, eg, 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, ie, “moral hazard.”<sup>12</sup> Hence, screening programs and conceptions of cancer may change conceptions of self and alter our ways of communicating.<sup>119</sup>

### 3.12 | 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 “CRC 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.<sup>21</sup>

### 3.13 | 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 reduction)<sup>166</sup> and that CRC screening touches on legal provisions regarding confidentiality of patients and other human rights issues.<sup>151</sup>

### 3.14 | Cut-offs and incidental findings

One of the identified challenges is to decide on cut-off values,<sup>34,167</sup> eg, 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.

## 4 | 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.<sup>168,169</sup> 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 informed consent has obtained much attention in general.

A wide range of relevant related issues have not been addressed in this review, eg, 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, eg, whether to assess and inform about screening programs on the basis of relative or absolute CRC risk reduction.<sup>170,171</sup> However, such questions have strong moral bearings, which it is important to acknowledge to facilitate an open and transparent deliberation. Informing the public that CRC screening reduces mortality (in general) may be misleading.<sup>79</sup>

Most of the identified ethical issues are covered by the questions of the axiological method,<sup>6</sup> but not all, eg, some of the practical challenges are not explicitly included in the questions. Moreover, several of the questions address issues not found in the literature, eg, whether it affects religious convictions, and whether screening would increase the status and prestige of the disease. Other methods for addressing ethical issues<sup>172</sup> could of course have been applied. However, this review has identified a series of other ethical issues than previous studies<sup>5</sup> and is in line with other studies on ethics in screening.<sup>31,173</sup>

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 implementation,<sup>154–156</sup> neither does a review of the ethical issues, ie, there is *no ethical "imperative of evidence."* Nonetheless, the review can prepare and facilitate this process.

## 5 | 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 because of 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, eg, in the

question of which groups should be offered which screening (age, sex, and 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 to 1 will die, to prevent 157 to die from CRC for every 100 000 persons invited, without reducing the overall mortality rate.

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## APPENDIX A

### Appendix: search strategy Ethics in CRC screening

Performed by Ingvild Kirkehei, Norwegian Institute for Public Health, Oslo

Performed: June 24, 2016

#### 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 strategy

The search strategies were elaborated for each database, because of 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 the systematic review by Fretheim et al referred to in the article. The searches resulted in 1120 references, 870 after removing duplicates.

#### ISI web of knowledge

References found: 196

# 4 #2 OR #1 Refined by: Databases: (WOS)

# 3 #2 OR #1

# 2 TITLE: ("colorectal cancer") AND TITLE: ("screening" or "colonoscop\*" or "Colonograph\*" or "sigmoidoscop\*" or "ifobt\*" or "fobt\*" or "occult blood" or "stool\*" or "fecal" or "faecal") AND TITLE: ("autonomy" or "self-determination" or "privacy" or "confidentiality" or "authenticity" or "agency" or "dignity" or "integrity" or "self-conception" or "selfness" or "personhood" or "vulnerability" or "medicalization" or "lifestyle" or "human rights" or "norm\*" or "priority" or "prioritization" or "equality" or "equity" or "justice" or "religio\*" or ("risk\*" and "benefi\*") or "stakeholder\*" or "informed consent" or "understanding" or "voluntariness" or "nudging" or "legal" or "legislation\*" or "regulation\*" or "false positive\*" or "false negative\*" or "predictive value\*" or "medicalization" or "overdiagnosis" or "over diagnosis" or "overtreatment" or "over treatment\*" or "target group\*" or "dual use")

# 1 TOPIC: ("colorectal cancer") AND TOPIC: ("screening" or "colonoscop\*" or "Colonograph\*" or "sigmoidoscop\*" or "ifobt\*" or "fobt\*" or "occult blood" or "stool\*" or "fecal" or "faecal") AND TOPIC: ("ethic\*" or "moral\*")

## MEDLINE (Ovid)

### Epub Ahead of Print, In-Process and Other Nonindexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

References found: 407

1. exp Colorectal Neoplasms/ or ((colorectal\* or colon\*) adj2 (cancer\* or neoplasm\* or tumor\* or carcinoma\*).tw.

2. colonoscopy/ or Colonography, Computed Tomographic/ or sigmoidoscopy/ or Occult Blood/ or exp Biomarkers, Tumor/bl or Immunochemical/ or Mass screening/ or Early Detection of Cancer/ or (colonoscop\* or Colonograph\* or sigmoidoscop\* or ifobt\* or fobt\* or (occult\* adj2 blood\*) or stool\* or fecal or faecal or (DNA and blood) or (biomarker\* adj3 (blood\* or tumor\* or molecular)) or screening or screen\* for or immunochem\* or immunol\*).tw. or detect\*.ti.

3. exp Ethics/ or morale/ or morals/ or moral development/ or (ethic\* or moral\* or challenges).tw.

4. (autonomy or self-determination or privacy or confidentiality or authenticity or agency or dignity or integrity or self-conception or selfness or personhood or vulnerability or medicalization or lifestyle or human rights or norm\* or value\* or priority or prioritization or equality or equity or justice or religio\* or (risk\* and benefi\*) or safety or stakeholder or information or informed or understanding or voluntariness or nudging or bias or legal or legislation\* or regulation\* or guideline\* or false positive\* or false negative\* or predictive value\* or medicalization or overdiagnosis or over diagnosis or overtreatment or over treatment\* or target group\* or subgroup\* or "dual use").tw

5. personal autonomy/ or exp Privacy/ or exp Confidentiality/ or personhood/ or exp Self Concept/ or Medicalization/ or Life Style/ or exp Human Rights/ or Social Norms/ or Social Values/ or Health Priorities/ or Health Equity/ or social justice/ or exp Religion/ or Risk Assessment/ or exp Safety/ or exp Access to Information/ or exp Consumer Health Information/ or Informed Consent/ or awareness/ or comprehension/ or consciousness/ or exp "bias (epidemiology)" or legal cases/ or legislation/ or social control, formal/ or government regulation/ or exp guideline/ or Guideline Adherence/ or exp Diagnostic Errors/ or "Predictive Value of Tests"/ or exp Medical Overuse/

6. or/4-5

7. 1 and 2 and 3 and 6

8. exp \*Ethics/ or \*morale/ or \*morals/ or \*moral development/ or (ethic\* or moral\* or challeng\*).ti.

9. 1 and 2 and 8

10. 7 or 9

11. (colorectal cancer and screening and (autonomy or self-determination or privacy or confidentiality or authenticity or agency or dignity or integrity or self-conception or selfness or personhood or vulnerability or medicalization or lifestyle\* or human rights or norm\* or social value\* or priority or prioritization or equality or equity or justice or religio\* or (risk\* and benefi\*) or stakeholder or informed consent or understanding or voluntariness or nudging or legal or legislation\* or regulation\* or false positive\* or false negative\* or predictive value\* or medicalization or overdiagnosis or over diagnosis or overtreatment or over treatment\* or target group\* or "dual use").ti.

13. 10 or 11

**EMBASE (Ovid)****1980 to 2016 Week 25**

References found: 159

1. (((colorectal\* or colon\*) adj2 (cancer\* or neoplasm\* or tumor\* or carcinoma\*)) and (colonoscop\* or Colonograph\* or sigmoidoscop\* or ifobt\* or fobt\* or (occult\* adj2 blood\*) or stool\* or fecal or faecal or DNA or immunol\* or immunochem\* or DNA\* or (biomarker\* adj3 (blood\* or tumor\*)) or screening or screen\* for)).tw.

2. (ethic\* or moral\*).mp.

3. (autonomy or self-determination or privacy or confidentiality or authenticity or agency or dignity or integrity or self-conception or self-ness or personhood or vulnerability or medicalization or lifestyle or human rights or norm\* or value\* or priority or prioritization or equality or equity or justice or religio\* or (risk\* and benefi\*) or safety or stakeholder or information or informed or understanding or voluntariness or nudging or bias or legal or legislation\* or regulation\* or guideline\* or false positive\* or false negative\* or predictive value\* or medicalization or overdiagnosis or over diagnosis or overtreatment or over treatment\* or target group\* or subgroup\* or "dual use").mp.

4. 1 and 2 and 3

5. (ethic\* or moral\*).ti. or \*ethics/ or \*bioethics/ or \*ethical theory/ or exp \*medical ethics/ or \*research ethics/ or \*morality/

6. 1 and 5

7. 4 or 6

8. limit 7 to embase

**PsycINFO (Ovid)****1806 to June Week 3 2016**

References found: 134

1. (((colorectal\* or colon\*) adj2 (cancer\* or neoplasm\* or tumor\* or carcinoma\*))).tw.

2. (colonoscop\* or Colonograph\* or sigmoidoscop\* or ifobt\* or fobt\* or (occult\* adj2 blood\*) or stool\* or fecal or faecal or (DNA and blood) or (biomarker\* adj3 (blood\* or tumor\* or molecular)) or screening or screen\* for or immunochem\* or immunol\*).tw. or detect\*.ti.

3. exp CANCER SCREENING/ or exp SCREENING/ or exp SCREENING TESTS/

4. 2 or 3

5. 1 and 4

6. exp ethics/

7. morality/ or dignity/ or integrity/ or exp justice/ or moral development/ or personal values/ or exp religious beliefs/ or social values/ or exp values/ or virtue/

8. (ethic\* or moral\*).tw.

9. (autonomy or self-determination or privacy or confidentiality or authenticity or agency or dignity or integrity or self-conception or self-ness or personhood or vulnerability or medicalization or lifestyle or human rights or norm\* or value\* or priority or prioritization or equality or equity or justice or religio\* or (risk\* and benefi\*) or safety or stakeholder or information or informed or understanding or voluntariness or nudging or bias or legal or legislation\* or regulation\* or guideline\* or false positive\* or false negative\* or predictive value\* or medicalization

or overdiagnosis or over diagnosis or overtreatment or over treatment\* or target group\* or subgroup\* or "dual use").ti.

10. 6 or 7 or 8 or 9

11. 5 and 10

**PubMed Bioethics subset**

References found: 156

("colorectal cancer" OR "colon cancer") AND screening AND bioethics [sb] AND (autonomy or "self-determination" or privacy or confidentiality or authenticity or agency or dignity or integrity or "self-conception" or selfness or personhood or vulnerability or medicalization or lifestyle or "human rights" or norm\* or value\* or priority or prioritization or equality or equity or justice or religio\* or (risk\* and benefi\*) or safety or stakeholder or information or informed or understanding or voluntariness or nudging or bias or legal or legislation\* or regulation\* or guideline\* or "false positive" or "false negative" or predictive value\* or medicalization or overdiagnosis or overtreatment or target group\* or subgroup\* or "dual use")

**BELIT—Bioethics Literature Database**Searched via [http://www.drze.de/belit-1/belit?set\\_language=en](http://www.drze.de/belit-1/belit?set_language=en)

References found: 57

Advanced search

Everywhere: «colorectal cancer»

Everywhere: screening

Combined with AND

**ETHMED—Ethics in Medicine**Searched via <http://www.idem.uni-goettingen.de/en/ethmed.html>

References found: 3

Search 1: rectal AND cancer AND screening

Search 2: colorectal AND cancer AND screening

**SIBIL—Base dati di bioetica**Searched via [http://www.iss.it/site/SebinaOpac\\_sedo/Opac?locale=en\\_GB](http://www.iss.it/site/SebinaOpac_sedo/Opac?locale=en_GB)

References found: 0

Search 1: Word search: colorectal cancer AND screening

Search 2: Word search: cancer AND screening

**LEWI—Bibliographic Database on Ethics in the Sciences and Humanities**Searched via [http://lewi.izew.uni-tuebingen.de/lewi/assoziativ\\_en.html](http://lewi.izew.uni-tuebingen.de/lewi/assoziativ_en.html)

References found: 7

Quick search: cancer screening

**EuroEthics**Searched via EthicsWeb <http://www.ethicsweb.eu/node/1>

Search 1: "colorectal cancer" AND screening

No new findings beyond PubMed.

Search 2: «Colon cancer» AND screening

1 new finding beyond PubMed

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# Author Query Form

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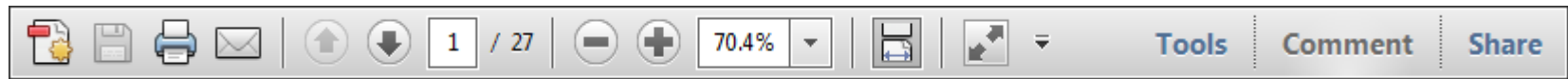
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| Q4        | AUTHOR: Please check all section headings if these are presented in their appropriate section levels.  |  |
| Q5        | AUTHOR: Please check Figure 1 caption if it is presented correctly.  |  |
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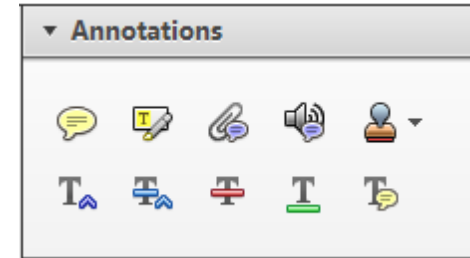
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This will open up a panel down the right side of the document. The majority of tools you will use for annotating your proof will be in the **Annotations** section, pictured opposite. We've picked out some of these tools below:



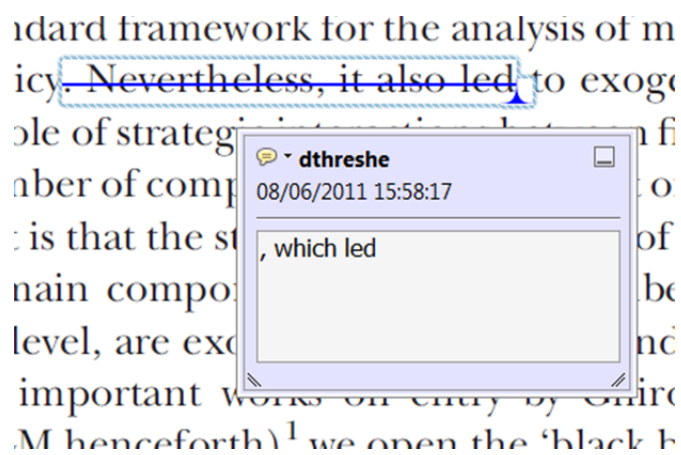
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Strikes a line through text and opens up a text box where replacement text can be entered.

**How to use it**

- Highlight a word or sentence.
- Click on the **Replace (Ins)** icon in the Annotations section.
- Type the replacement text into the blue box that appears.



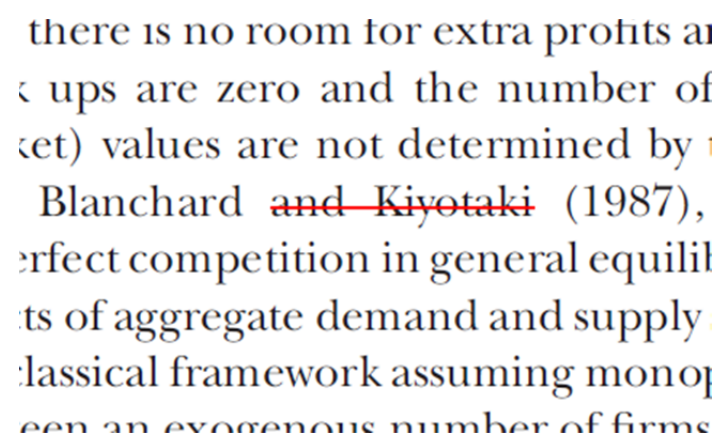
**2. Strikethrough (Del) Tool – for deleting text.**



Strikes a red line through text that is to be deleted.

**How to use it**

- Highlight a word or sentence.
- Click on the **Strikethrough (Del)** icon in the Annotations section.



**3. Add note to text Tool – for highlighting a section to be changed to bold or italic.**

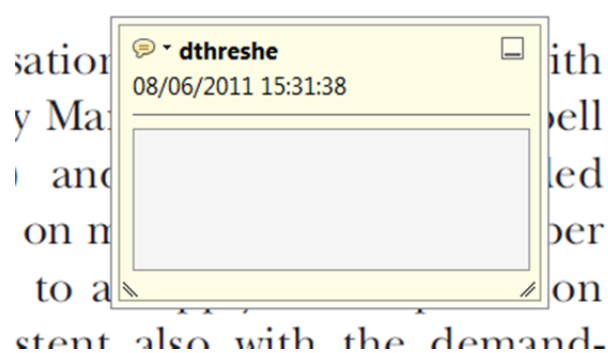


Highlights text in yellow and opens up a text box where comments can be entered.

**How to use it**

- Highlight the relevant section of text.
- Click on the **Add note to text** icon in the Annotations section.
- Type instruction on what should be changed regarding the text into the yellow box that appears.

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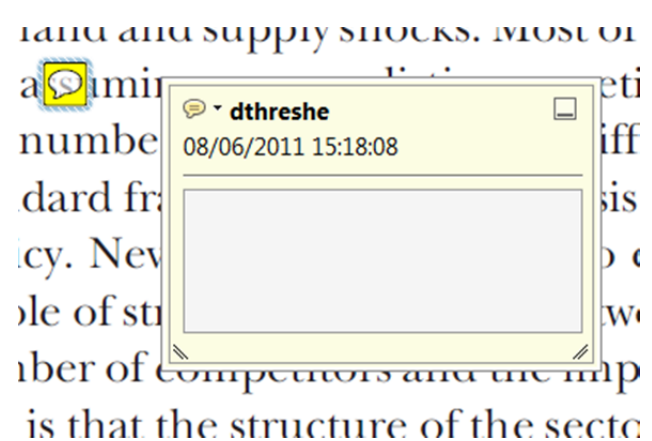
**4. Add sticky note Tool – for making notes at specific points in the text.**



Marks a point in the proof where a comment needs to be highlighted.

**How to use it**

- Click on the **Add sticky note** icon in the Annotations section.
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the yellow box that appears.



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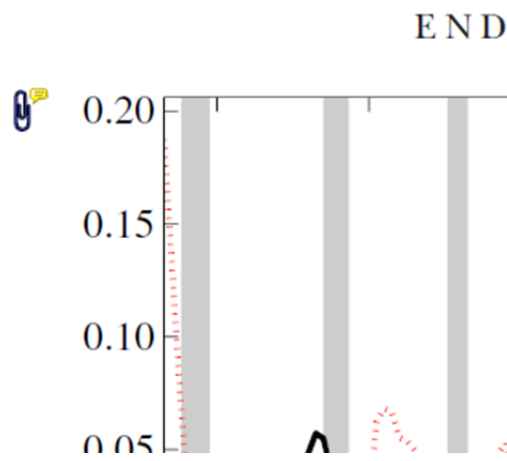
**5. Attach File Tool – for inserting large amounts of text or replacement figures.**



Inserts an icon linking to the attached file in the appropriate place in the text.

**How to use it**

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- Click on the proof to where you'd like the attached file to be linked.
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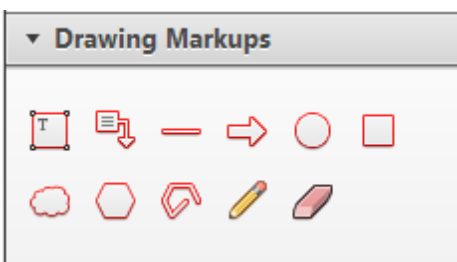


Inserts a selected stamp onto an appropriate place in the proof.

**How to use it**

- Click on the [Add stamp](#) icon in the Annotations section.
- Select the stamp you want to use. (The [Approved](#) stamp is usually available directly in the menu that appears).
- Click on the proof where you'd like the stamp to appear. (Where a proof is to be approved as it is, this would normally be on the first page).

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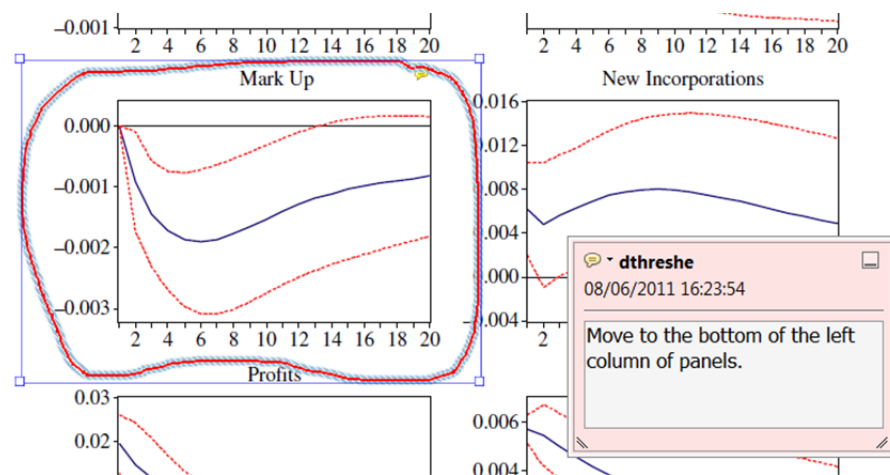


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- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
- Double click on the shape and type any text in the red box that appears.



For further information on how to annotate proofs, click on the [Help](#) menu to reveal a list of further options:

