Screening for colorectal cancer in people with a familial risk[1]

EXTRACT

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Involvement of affected people

People with a familial risk of colorectal cancer were consulted during the preparation of the report. The aim of this discussion was to obtain information on the following topics: expectations of the screening procedure and motivation to participate, experiences with the procedure, consequences of results and concerns regarding the procedure. Two affected people took part in the discussion. IQWiG thanks them for their participation. They were not involved in the preparation of the report.

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Early Detection of Cancer, Mass Screening, Colorectal Neoplasms, Family History, Benefit Assessment, Systematic Review

Key statement

Research question

The aim of this investigation is to assess screening for CRC in people under the age of 50 with a familial risk. This objective was broken down into the following sub-objectives:

- Sub-objective 1: To compare the benefits and harms of CRC screening with no screening in people under 50 years of age with a familial risk of CRC.

- Sub-objective 2: To assess the transferability of findings on CRC screening in the general population aged 50 and over to people under 50 with a familial risk of CRC.

Sub-objective 2 was to be addressed if no (meaningful) evidence was identified for sub-objective 1.

Conclusion

Direct evidence on CRC screening in people under 50 with a familial risk of CRC

There is no direct evidence on the systematic screening of people under the age of 50 with a familial risk of CRC (there are no comparative intervention studies of the screening process).

Indirect evidence on CRC screening (transferability)

An extensive search for studies on the transferability of CRC screening findings from people aged 50 and over without a (known) familial risk of CRC to people under 50 with a familial risk overall revealed little evidence on individual aspects of transferability.

Only one aspect of transferability — namely, the diagnostic accuracy and direct adverse effects of established screening tests — is supported by the identified evidence on transferability. For the other transferability aspects, the identified evidence neither supports nor refutes transferability, or there is no evidence. Therefore, in the overall assessment of the rather sparse evidence on key transferability aspects, it remains unclear whether the proven benefits of CRC screening for people aged 50 years or older without a (known) familial risk of CRC could be achieved in a similar way in people under 50 years of age with a familial risk.

Recommendations for an accompanying assessment in the event of an extension of CRC screening

If despite the limited evidence, CRC screening is introduced in Germany for people under 50 with a familial risk of CRC, an accompanying assessment should be carried out. For example, a comparison could be made with another country where no such risk group screening has been established. This report contains detailed recommendations for designing such an assessment.

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List of abbreviations

Abbreviation	Meaning
CI	confidence interval
CRC	colorectal cancer
EGFR	epidermal growth factor receptor
FAP	familial adenomatous polyposis
FOBT	faecal occult blood test
G-BA	Federal Joint Committee (Gemeinsamer Bundesausschuss)
gFOBT	guaiac faecal occult blood test
HNPCC	hereditary non-polyposis CRC
HTA	health technology assessment
IDR	incidence density ratio
iFOBT	immunological faecal occult blood test
IQWiG	Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
OR	odds ratio
PLCO	Prostate, Lung, Colorectal and Ovarian (Cancer Screening Trial)
RCT	randomized controlled trial
SSL	sessile serrated lesion

1 Background

Colorectal cancer (CRC) is estimated by the International Agency for Research on Cancer (2020) to be the second most common cancer in women and the third most common cancer in men worldwide among all new cancers [1]. For both women and men, CRC was estimated to be the third most common cause of cancer death [1]. According to data from the Robert Koch Institute (RKI), this situation also applies to both women and men in Germany [2].

In around 70% of cases, CRC develops from slow-growing, initially benign neoplasms (adenomas) that form in the mucosa of the colon and rectum and are often polypoid [3,4]. According to the adenoma-carcinoma sequence model [5], adenomas can grow through various stages, invade the deeper layers of the intestinal wall and become malignant. In addition, 25% to 30% of CRCs develop on the base of sessile serrated lesions (SSLs), i.e. through the SSL carcinoma pathway [4]. Screening tests for CRC have 2 objectives: One is to detect and remove adenomas before they become malignant. Secondly, carcinomas should be identified before they become symptomatic and metastasize. As a result, morbidity, in particular the rate of new cases of CRC, and (CRC-specific) mortality should be reduced [6].

In Germany, organized CRC screening is currently offered to people with statutory health insurance from the age of 50. From this age, women and men have the option of screening using an immunological faecal occult blood test (iFOBT). From this age, men have the alternative of early detection by means of colonoscopy. From the age of 55, both sexes can choose between iFOBT and colonoscopy. If the result of the iFOBT is positive, there is an entitlement to a colonoscopy for clarification. The entitlement to colonoscopies as a screening examination is limited to a total of 2, with the second being carried out at the earliest 10 years after the first [6].

In addition to the iFOBT and colonoscopy, there are other screening methods such as sigmoidoscopy as an alternative endoscopic procedure (colonoscopy of the sigmoid and rectum) or the guaiac FOBT (gFOBT), the predecessor of the iFOBT [7].

If adenomas, SSLs or early carcinomas are identified during an endoscopic (screening) examination, the lesion is completely removed (polypectomy), if possible, during the same or a subsequent colonoscopy session with subsequent follow-up colonoscopies. If CRC is identified in the course of these examinations, treatment consists of endoscopic or surgical tumour resection, which may be followed by adjuvant chemotherapy. Depending on the location, neoadjuvant radiochemotherapy may be necessary for rectal cancer before surgery, but there is also the option of total neoadjuvant therapy with organ preservation [7-9].

Current CRC screening in Germany is a population-wide screening programme. There is currently no organized CRC screening specifically for risk groups. There are several groups of

people for whom a familial risk of CRC is known. One of the currently known risk groups is people who have at least one first or second degree relative with CRC without a known genetic cause [7] (also known as people with a positive family history). This group of people has an approx. 2-fold to approx. 4-fold higher risk of developing CRC than people without a positive family history [10,11]. In this case, we therefore speak of people with a familial risk of CRC. As screening is only available from the age of 50, people with a familial risk of CRC under the age of 50 are currently not entitled to participate in organized CRC screening.

Other known risk groups include people with hereditary diseases such as Lynch syndrome (formerly known as hereditary non-polyposis CRC [HNPCC]) or familial adenomatous polyposis (FAP) as well as people with chronic inflammatory bowel disease. These risk groups have their own recommendations for the screening and prevention of CRC [7]. They are therefore not examined in this report.

This assessment aims to answer the question of what is known about the benefits and harms of CRC screening in people under 50 years of age with a familial risk of CRC. This question was already part of the previous benefit assessments S11-01 [10] and S17-01 [12] by the Institute for Quality and Efficiency in Health Care (IQWiG). In both benefit assessments, the benefits and harms of CRC screening in people with a familial risk of CRC remained unclear due to a lack of (suitable) data.

In view of the lack of evidence on the benefits and harms of CRC screening in this group of people, the final report S11-01 outlined a possible alternative assessment path in addition to the search for comparative intervention studies of the screening chain, namely the systematic and evidence-based answer to the question of whether findings on the benefits of CRC screening in the general population can be transferred to the group of people under 50 years of age with a familial risk. It was stated that, among other things, it would be necessary to assess whether the adenoma-carcinoma sequence (from today's perspective, to be supplemented by the SSL carcinoma pathway), the detectability of adenomas, the treatability of carcinomas, and the occurrence of complications during endoscopic screening are comparable in the two groups of people [10].

In addition to an update of certain questions of the benefit assessment of CRC screening in people under 55 years of age with a familial risk of CRC in Project S17-01, this report examines the extent to which transferability of findings on CRC screening in people aged 50 years or older without a familial risk of CRC to people under 50 years of age with a familial risk of CRC is given.

2 Research question

The aim of this investigation is to assess screening for CRC in people under the age of 50 with a familial risk. This objective was broken down into the following sub-objectives:

- Sub-objective 1: To compare the benefits and harms of CRC screening with no screening in people under 50 years of age with a familial risk of CRC.
- Sub-objective 2: To assess the transferability of findings on CRC screening in the general population aged 50 and over to people under 50 with a familial risk of CRC.

Sub-objective 2 was to be addressed if no (meaningful) evidence was identified for sub-objective 1.

3 Methods

The aim was to assess screening for CRC in people under the age of 50 with a familial risk of CRC. The assessment was pursued in 2 sub-objectives:

Sub-objective 1 was to assess the benefits and harms of CRC screening compared to no specific CRC screening in people under 50 years of age with a familial risk of CRC. Here, comparative intervention studies of the screening chain in people under 50 years of age with a familial risk were included, in which CRC screening was compared with no specific CRC screening with regard to patient-relevant outcomes. Randomized controlled trials (RCTs), quasi-randomized controlled trials, and prospective comparative cohort studies were included

The following patient-relevant outcomes were considered:

- Overall survival
- Disease-specific (tumour-specific) survival
- Occurrence of CRC
- Occurrence of advanced adenomas
- Occurrence of advanced SSLs
- Health-related quality of life and psychosocial aspects
- Harms resulting directly and indirectly from the CRC screening test or from subsequent diagnostic examinations, including the consequences of false screening results and overdiagnosis

If no (meaningful) evidence could be identified for sub-objective 1, an assessment of the transferability of findings on CRC screening in the normal population of at least 50 years of age to people under 50 years of age with a familial risk was planned (sub-objective 2). Instead

of the term "normal population", the term "general population" is used in the following. The general population refers to people without a specifically increased risk of CRC or people who are not known to have a familial risk of CRC. The following points were considered:

- Effects of CRC screening in comparative intervention studies of the screening chain (sub-objective 2a)
- Findings on the (natural) course of CRC (sub-objective 2b)
- Data on the diagnostic accuracy and direct (adverse) effects of the established screening tests (sub-objective 2c)
- Data on CRC treatment in people with a familial risk of CRC (sub-objective 2d)

With regard to the individual sub-objectives, the aim was to compare people with and without a familial risk of CRC.

Parallel to the preparation of the protocol (“report plan”), a search for systematic reviews was carried out in the MEDLINE database (including the Cochrane Database of Systematic Reviews) and the Health Technology Assessment (HTA) database, as well as on the websites of the National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ).

The systematic literature search for studies for sub-objective 1 and sub-objective 2a was carried out in the databases MEDLINE, Embase, the Cochrane Central Registry of Controlled Trials, and the International HTA Database for systematic reviews / HTAs.

In addition, the following sources of information and search techniques were taken into account: study registries and the inspection of reference lists.

Depending on the results identified, a focused search for systematic reviews or studies for sub-objectives 2b, 2c and 2d was also carried out in bibliographic databases, study registries and other sources.

The selection of relevant studies was carried out by 2 people independently of each other. Discrepancies were resolved by discussion. Data were extracted into standardized tables. Across-outcome and outcome-specific risk-of-bias criteria were assessed to assess the qualitative certainty of results, and the risk of bias was rated as low or high in each case. No specific assessment and documentation of the risk of bias was carried out for the studies on sub-objective 2, as no classification of the certainty of conclusions was made in the assessment of transferability. The results of the individual studies were described according to outcomes.

In addition to the comparison of the results of the individual studies, meta-analyses and sensitivity analyses were performed and effect modifiers examined, provided that the methodological requirements were met.

For sub-objective 1, a conclusion on evidence of (greater) benefit and (greater) harm was drawn in 4 grades regarding the respective certainty of conclusions: either proof (highest certainty of conclusions), an indication (moderate certainty of conclusions), a hint (weakest certainty of conclusions), or none of these 3 situations was present. The latter case occurred when no data were available or the available data did not allow any of the other 3 conclusions. In this case, the conclusion "There is no hint of (greater) benefit or (greater) harm" was drawn. Finally, an assessment of benefit and harm across outcomes was performed.

For sub-objective 2, for each transferability aspect (sub-objectives 2b to 2d), the extent to which people under the age of 50 with a familial risk are comparable with people from the general population aged at least 50 with regard to the aspect under consideration was first assessed. In order to be able to assume transferability for each of the transferability aspects, meaningful evidence had to be available for all sub-aspects relevant to the transferability aspect that supported transferability. Results supporting transferability were results that indicated a comparability of people with and without risk with regard to the sub-aspects under consideration. The following specifications applied for each transferability aspect:

- Transferability aspect: findings on the (natural) course of CRC
  - In order to be able to assume transferability for the natural course, meaningful data had to be available for all particularly important characteristics that describe the natural course of CRC, indicating comparability. This includes the risk of degeneration or the rate of progression of precancerous lesions, the risk of metastasis and symptoms associated with precancerous lesions and carcinomas.
- Transferability aspect: Diagnostic accuracy and direct (adverse) effects of the established screening tests
  - In order to be able to assume overall transferability for this transferability aspect, data had to be available on both the diagnostic accuracy and the direct (adverse) effects of the established screening tests that indicated comparability for at least 1 of the established screening tests.
- Transferability aspect: CRC treatment in people with a familial risk of CRC
  - Evidence had to be available for at least 1 non-drug intervention (e.g. resection of the primary tumour, radiofrequency ablation of liver metastases, etc.) and one drug therapy (e.g. chemotherapy, anti-epidermal growth factor receptor [EGFR] antibodies, etc.) that indicates comparability.

Comparative intervention studies of the screening chain in people aged at least 50 years with a familial risk (sub-objective 2a) could have yielded findings on the effect of CRC screening. However, an effect of CRC screening in people under 50 years of age with a familial risk could only have been assumed on the basis of these studies if the investigation of the other transferability aspects (sub-objectives 2b to 2d) had shown that overall, transferability of findings on CRC screening in people of at least 50 years of age without a familial risk to people under 50 years of age with a familial risk can be assumed.

If the conclusion on transferability for a transferability aspect was also based on studies in which only people aged 50 years or older were included, other studies on this transferability aspect had to show that the relevant findings also apply to people under 50 years of age with a familial risk.

Evidence that spoke against transferability for one of the transferability aspects regularly led to no transferability being assumed across all transferability aspects.

Taking into account the evidence on all aspects of transferability, it was then assessed whether the identified evidence overall speaks for or against the transferability of findings on CRC screening in the general population of at least 50 years to people under 50 years with a familial risk or whether this must remain open due to missing or ambiguous results. In order to be able to assume overall transferability, meaningful evidence had to be available for all aspects of transferability, each of which supported transferability. If, in the overall assessment, the evidence identified supported or did not support transferability (i.e. the question of transferability did not have to remain open), it was then examined whether the results imply a more favourable or less favourable benefit-harm ratio in people with a familial risk of CRC compared to people without such a risk.

4 Results

4.1 Results of information retrieval

The comprehensive information retrieval yielded the following results:

- Sub-objective 1 (comparative intervention studies of the screening chain in people under 50 with a familial risk):
  - No relevant study
- Sub-objective 2a (comparative intervention studies of the screening chain in people of at least 50 years of age with a familial risk):
  - 1 relevant RCT

One ongoing study was identified.

The search strategies for bibliographic databases and study registries can be found in the appendix. The last search took place on 29 February 2024.

The additional focused search for systematic reviews or studies yielded the following results:

- Sub-objective 2b (studies on the [natural] course of CRC in people with a familial risk):
  - 1 relevant systematic review
- Sub-objective 2c (studies on the diagnostic accuracy and adverse effects of screening tests in people with a familial risk):
  - 5 relevant studies on diagnostic accuracy and adverse effects
- Sub-objective 2d (studies on CRC treatment in people with a familial risk):
  - No relevant study

The search strategies for bibliographic databases and study registries can be found in the appendix. The last search took place on 28 March 2024.

Table 1: Study pool of the benefit assessment

Study	Available documents			
	Full publication (in scientific journals)	**Registry entry / results report from study registries**	**Study report from manufacturer documents (not publicly accessible)**	**Other documents**
Sub-objective 1: Comparative intervention studies of the screening chain in people under 50 with a familial risk				
-	-	-	-	-
Sub-objective 2a: Comparative intervention studies of the screening chain in people aged at least 50 with a familial risk				
PLCO[a]	yes [13]	no	no	no
Sub-objective 2b: Systematic review of the (natural) course of CRC in people with a familial risk				
Henrikson 2015[b]	yes [14]	no	no	no
Sub-objective 2c: Studies on the diagnostic accuracy and adverse effects of screening tests in people with a familial risk				
Cha 2012[a]	yes [15]	no	no	no
Cubiella 2014[a]	yes [16]	no	no	no
Hilsden 2015[c]	yes [17]	no	no	no
Jung 2020[a]	yes [18]	no	no	no
Ng 2013[a]	yes [19]	no	no	no
Sub-objective 2d: Studies on CRC treatment in people with a familial risk				
-	-	-	-	-

- No relevant study identified.
a. Primary study.
b. Systematic review.
c. Study did not meet the inclusion criteria, but was used as supplementary information for sub-objective 2c to assess the adverse effects of screening tests.

CRC: colorectal cancer; PLCO: Prostate, Lung, Colorectal and Ovarian (Cancer Screening Trial)

4.2 Sub-objective 1: Comparative intervention studies of the screening chain in people under 50 with a familial risk

No relevant study was identified for sub-objective 1. There is therefore no hint of benefit or harm of CRC screening in people under 50 years of age with a familial risk.

4.3 Sub-objective 2a: Comparative Intervention studies of the screening chain in people aged at least 50 with a familial risk

For sub-objective 2a, the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial [13], an intervention study of the screening chain was identified.

4.3.1 Characteristics of the studies included in the assessment

The PLCO trial (publication with relevant results for the present assessment: Schoen 2015 [13]) is a multicentre RCT in which the study participants were randomized to screening by sigmoidoscopy in the intervention arm or to standard care in the control arm. The study is part of the overall PLCO trial, which also investigated screening for cancers of the lung, prostate and ovaries. The study was conducted from 1993 to 2001 in 10 screening centres in the USA and included a follow-up of up to 13 years. The study included men and women between the ages of 55 and 74 who had not been diagnosed with CRC. From 1995 onwards, people who had undergone a colonoscopy, sigmoidoscopy or colon contrast enema in the last 3 years were also excluded. Study participants were recruited through targeted letters sent to people identified from publicly available, commercial or study centre address lists.

In the intervention arm, a sigmoidoscopy was performed for early detection of CRC at baseline and after 3 years (study inclusion before 04/1995) or after 5 years (study inclusion after 04/1995). The participants and their doctors were informed about pathological findings during the sigmoidoscopy; further diagnostics and, if necessary, treatment took place outside the study. In the control arm, no CRC screening was carried out beyond standard care ("usual care"), which did not vary during the study. In the control arm, a sigmoidoscopy or colonoscopy was performed in approx. 47% of the people during the screening phase, and a colonoscopy was performed in 48% after the end of the screening phase.

The primary outcome was disease-specific mortality, in relation to CRC screening the CRC-specific mortality (defined as deaths due to CRC or as a result of CRC treatment). Secondary outcomes included in particular the occurrence of CRC, overall mortality, tumour stage and screening-related adverse events. The data were collected through annual questionnaires of the study participants (with the help of population-based cancer registries and official death data with validation of the documented causes of death by reviewing death certificates and autopsy reports, among other things).

Of the 154,900 people originally included, 144,768 had a complete family history, which was recorded at baseline using a questionnaire. A familial risk of CRC was defined as having at least one first-degree relative who had been diagnosed with CRC (no definition of age of onset). 14,961 people (10.3% of all people analysed) had a familial risk of CRC. 129,808 (89.7%) people had no familial risk of CRC. (In the Schoen 2015 publication, 144,768 people were analysed; however, the sum of people with and without a familial risk of CRC is 144,769 people).

4.3.2 Overview of patient-relevant outcomes

Data on patient-relevant outcomes were included from 1 study (PLCO trial). Table 2 shows an overview of the available data on patient-relevant outcomes from the included study. Usable data were reported for the outcomes of disease-specific mortality and occurrence of CRC for

the general population (results on the effect between people with and people without a familial risk of CRC). The outcomes "overall survival / all-cause mortality", "tumour / cancer stage" and "harms of screening" were collected as secondary outcomes, but it was not announced that these outcomes would be analysed for effect differences between people with and without familial risk of CRC. (Results on these outcomes were therefore not available.) No data were reported on the outcomes “occurrence of advanced adenomas”, “occurrence of advanced SSLs”, “health-related quality of life”, “consequences of incorrect screening findings” and “overdiagnosis”.

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes									
	Mortality	Morbidity					HrQoL	Adverse effects		
	Overall survival	Disease-specific (tumour-specific) mortality	Occurrence of CRC	Occurrence of advanced adenomas	Occurrence of advanced SSLs	Tumour stage	Health-related quality of life and psychosocial aspects	Harms caused by tests / subsequent examinations	Consequences of false screening results	Overdiagnosis
PLCO	-[a]	●	●	-	-	-[a]	-	-[a]	-	-

●: Data reported and usable.
-: No data reported (no further details).
a. No results for sub-objective 2a: It was stated that in addition to the occurrence of CRC, the outcomes "Overall survival / all-cause mortality", survival time, tumour / cancer stage and "harms of screening" were collected as secondary outcomes. However, it was not mentioned that an analysis of effect differences between people with and without a familial risk of CRC would be conducted for these outcomes.

CRC: colorectal cancer; HrQoL: health-related quality of life; PLCO: Prostate, Lung, Colorectal and Ovarian (Cancer Screening Trial); SSL: sessile serrated lesion

4.3.3 Results on patient-relevant outcomes

The only results from the PLCO trial relevant for the present assessment were on the two outcomes “CRC-specific mortality” and “occurrence of CRC” (results on the effect of family history within each of the two study arms; the effect of screening was not reported separately for people with and people without a familial risk).

4.3.3.1 Results for CRC-specific mortality and occurrence of CRC

For the two outcomes “CRC-specific mortality” and “occurrence of CRC”, the time until the event occurred (death due to CRC or occurrence of CRC) was analysed for the subpopulations of people with and without a familial risk of CRC. The median follow-up time for people

without a familial risk of CRC was 11.8 years, and 12.5 years for those with a familial risk. The relevant result in the context of the present assessment is the data on the interaction between family history and study arm with regard to the time to a CRC diagnosis or to a CRC-specific death. With regard to both outcomes, the interaction mentioned was not statistically significant (p-value for the interaction regarding the occurrence of CRC: 0.84; p-value for the interaction regarding CRC-specific mortality: 0.73).

For the overall group, the number of patients with an event in relation to the person-time was analysed for both outcomes (incidence density). A statistically significantly lower CRC incidence was reported in the intervention arm compared with the control arm (incidence density ratio [IDR]: 0.79; 95% confidence interval [CI]: [0.72; 0.85]; $p < 0.001$). Statistically significantly fewer CRC deaths were also reported in the intervention arm compared with the control arm (IDR: 0.74; 95% CI: [0.63; 0.87]; $p < 0.001$). The effect estimates for the comparison of screening versus no screening were not reported differentiated by family history. Nevertheless, an estimate based on the available data for CRC incidence and CRC-specific mortality shows that the reported p-values for the interaction are not compatible with any relevant effect differences in people with and without a family history in relation to the point estimate and CI. The results of the PLCO trial thus suggest that the screening effect is not modified by family history in people aged 55 years and older (study population of the PLCO trial).

Summarized assessment

In the PLCO trial, there was a statistically significant effect in favour of screening in the general population with regard to CRC-specific mortality and occurrence of CRC. At the same time, there was no statistically significant interaction between family history and study arm for either outcome (i.e. no different effect of screening in people with and without a familial risk). The statistically non-significant interaction between family history and study arm therefore does not give rise to the assumption that screening could have a smaller effect in people with a positive family history, so that overall this does not argue against the transferability of the effect found in the general population to people under 50 years of age with a positive family history. However, there was no evidence from the assessment of the transferability aspects (sub-objectives 2b to 2d; see Chapter 5) that shows that results from people of at least 50 years of age are transferable to people under 50 years of age. For this reason, the effect modification not demonstrated in the PLCO trial cannot be transferred to the group of people under 50 years of age.

Overall, the results of the PLCO trial speak neither for nor against the transferability of findings on CRC screening in the general population of at least 50 years of age to people under 50 years of age with a familial risk of CRC, so that the question of the transferability of the effects of CRC screening must remain open.

4.4 Sub-objective 2b: Studies on the (natural) course of CRC in people with a familial risk

4.4.1 Description of the systematic reviews included in the assessment

For sub-objective 2b, 1 relevant systematic review was identified (Henrikson 2015) [14].

In Henrikson 2015, 4 sub-questions were examined, 1 of which related to the comparative assessment of the natural course of CRC in people with and without a familial risk of CRC. The other sub-questions related to the comparative assessment of the frequency of a familial risk of CRC, the level of risk for the development of adenomas or CRC, and colonoscopy adherence, and were therefore not relevant for the present assessment.

A total of 9 studies were included in Henrikson 2015 with regard to the sub-question on the natural course of disease.

For the assessment of the natural course of disease, we searched for studies that reported data on the following outcomes for adults with and without a familial risk of CRC:

- Proportion of people with (distal, proximal, advanced) adenomas
- Location of adenomas
- Location of carcinomas
- Tumour stage at CRC diagnosis
- Age at CRC diagnosis

The studies had to provide information on the age of onset of the relative(s) with adenoma or CRC, the number of affected relatives and the degree of relationship. RCTs, non-randomized comparative trials (controlled clinical trials, CCTs), cohort studies, studies based on population-based registries, case series ("case-only"), case-control studies ("case-control") and studies described as "case/case (study)" were considered. In addition, only studies in which a colonoscopy was performed in at least 500 study participants were included. Studies on people with hereditary CRC syndromes or with CRC associated with other diseases (e.g. Crohn's disease) were excluded.

The last literature search in the systematic review by Henrikson 2015 took place in February 2013.

The quality of the results from Henrikson 2015 was evaluated as part of this assessment using AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews 2). As a result, the reliability of the results was rated as low, but sufficient for the assessment of transferability.

In Henrikson 2015, it was stated that risk of bias of the included natural course studies were assessed using a self-designed checklist (e.g. regarding the type of family history recording

and the quality of outcome recording). The result of this assessment was reported in Henrikson 2015 only in summarized form and not for all included natural course studies. Therefore, the results of the assessment reported in Henrikson 2015 were reviewed only superficially. In the course of this, no deviations were discovered that would have cast doubt on the validity of the assessment in Henrikson 2015.

In each case, the conclusions on the outcomes considered were taken from Henrikson 2015. Of the 9 studies on natural course included in Henrikson 2015, only the results from 7 studies were included in the present assessment; 2 of the studies on natural course included in Henrikson 2015 were not relevant for the present assessment: In 1 study (Chan 2008), there were only data on the outcome “age at CRC diagnosis”, which was not relevant for the present assessment. Age at CRC diagnosis is not a characteristic that directly describes the natural course of CRC. It could be influenced not only by aspects of the natural course of disease (such as the rate of progression), but also by other factors (e.g. characteristics of the health care system: a different probability of diagnosis in people with and without a familial risk of CRC could thus lead to a different average age at CRC diagnosis). A non-relevant analysis was presented for 1 study (Lynch 2003). (Only the proportions of people with a familial risk of CRC were compared between people with no adenomas versus people with any adenomas versus people with advanced adenomas).

The 7 studies included were described in Henrikson 2015 as prospective cohort studies (Bass 2008, Kao 2009 and Wark 2009), as retrospective analyses of patient data (Hemminki 2010, Japanese Research Society 1993 and Zell 2008) and as a cross-sectional study (Hoffmeister 2010). The sample sizes ranged from 781 to 27,650 people. If reported, the mean or median age of the study participants was always over 60 years in the studies.

4.4.2 Overview of outcomes for natural course

Table 3 provides an overview of the outcomes that describe the natural course of disease for which data was available from the systematic review by Henrikson 2015. Data were available for 4 of the pre-specified outcomes (or categories of outcomes). No data were available for other relevant outcomes that describe the natural course of CRC development. The information on the outcome “age at CRC diagnosis” from Henrikson 2015 was not included in the present assessment, as it was not considered relevant for the assessment of transferability.

Table 3: Overview of outcomes on the natural course of disease for which results were reported from the included systematic review for the comparison between people with and without familial risk of CRC

Outcomes for natural course	Comparative data available
Type of precursor lesion or precancerous lesion (frequency)	●[a]
Regarding precancerous lesions:	
Detection rate	-
Degree of dysplasia	●[b]
Risk of degeneration	-
Progression speed	-
Regarding precancerous lesions and carcinomas:	
histopathological features	-
Macroscopic features	-
Location	●[c]
Symptoms	-
Regarding carcinomas:	
Tumour stage	●[d]
Lethality	-

●: Usable data was available.
-No data was available.
a. Proportion of people with adenomas, proportion of people with distal adenomas, proportion of people with proximal adenomas and proportion of people with advanced adenomas.
b. People with advanced adenomas.
c. Location of adenomas and location of carcinomas.
d. Tumour stage at CRC diagnosis.
CRC: colorectal cancer

4.4.3 Results on outcomes on the natural course of disease

For the outcomes on the natural course of disease, conclusions were excerpted from Henrikson 2015 that related to the comparison between people with and without a familial risk of CRC with regard to the respective outcome. The qualitative conclusions from Henrikson 2015 were always adopted and, where possible, additional quantitative information was provided.

Outcomes for which (statistically significant or numerical) differences were reported between people with and without a familial risk of CRC

According to the description in Henrikson 2015, there were statistically significant or numerical differences between people with and without a familial risk of CRC in all the studies included for each outcome : the proportion of people with adenomas (2 studies), the proportion of people with distal adenomas (1 study), the proportion of people with proximal adenomas (1 study), and the proportion of people with advanced adenomas (2 studies). (In

each case, the proportion of people with any adenomas - or with distal, proximal or advanced adenomas - in all people with a familial risk of CRC or in all people without such a risk was reported; in the following, for the sake of simplicity, only the proportion of people is referred to.

Both the proportion of people with adenomas and the proportion of people with distal adenomas were statistically significantly higher in people with a familial risk of CRC than in people without such a risk:

Any adenomas

In 1 study, 15.8% of people with at least 1 first-degree relative with CRC were diagnosed with an adenoma compared to 10% of people without a first-degree relative with CRC (odds ratio [OR] adjusted for various risk factors: 1.75; 95% CI: [1.60; 1.60]). In people with at least 2 first-degree relatives with CRC (OR adjusted for various risk factors: 1.75; 95% CI: [1.60; 1.91]); an adenoma was even detected in 19.1% (adjusted OR for the comparison with people without first-degree relatives: 2.36; 95% CI: [1.84; 3.04]). In 1 further study, the proportion of people with adenomas was numerically (but not statistically significantly) higher in people with at least 1 first-degree relative with CRC (40.2%) than in people without first-degree relatives or with CRC (30.5%).

Distal adenomas

A similar picture emerged with regard to distal adenomas (i.e. adenomas in the left hemicolon, i.e. adenomas in the descending colon or sigmoid colon): In 1 study, 3.4% of people with 1 first-degree relative with CRC were found to have at least 2 distal adenomas compared with 1.9% of people with no first-degree relatives with CRC (adjusted OR: 1.26; 95% CI: [1.02; 1.63]). (The proportion of people with at least 2 distal adenomas in people with at least 1 or at least 2 first-degree relatives with CRC was numerically higher than in people without a familial risk of CRC).

Proximal adenomas

With regard to the proportion of people with at least 2 proximal adenomas (i.e. adenomas in the right hemicolon, i.e. adenomas in the caecum, ascending colon, flexura hepatica, transverse colon or flexura coli sinistra), 1 study reported a numerical difference between people with and without a familial risk of CRC (proportion of people with at least 2 proximal adenomas numerically higher in people with a familial risk of CRC than in people without such a risk), but no information on the statistical significance of the difference was provided.

Advanced adenomas

A numerical (but not statistically significant) difference in the proportion of people with advanced adenomas was also reported in 2 studies between people with and without a

familial risk of CRC (7.7% in people with at least 1 first-degree relative with CRC compared with 5.0% in people without a first-degree relative with CRC; in the Hoffmeister 2010 study, 16.1% in people with at least 1 first-degree relative with CRC compared with 10.9% in people without a first-degree relative with CRC).

Outcomes for which either heterogeneous data or no differences between people with and without familial risk of CRC were reported

Location of carcinomas

With regard to the location of carcinomas , 2 studies reported that distal location of CRC was more common in people with a familial risk of CRC than in people without such a risk (no data on statistical significance); in 2 studies, however, no such correlation was observed.

Location of adenomas

With regard to the location of adenomas (1 study) and the tumour stage at CRC diagnosis (3 studies), the included studies showed no (statistically significant) differences between people with and without a familial risk of CRC, according to the description in Henrikson 2015.

Tumour stage at CRC diagnosis

With regard to tumour stage at CRC diagnosis, the 3 included studies did not show a different distribution of tumour stages between people with and without familial risk of CRC, according to the description in Henrikson 2015. Table 4 shows for which of the outcomes on the natural course of disease the studies included in Henrikson 2015 indicated differences between people with and without a familial risk of CRC, and for which outcomes this was not the case.

Summarized assessment

The fact that a higher proportion of people with adenomas was found in people with a familial risk of CRC than in people without such a risk is a difference that indicates the transferability of findings on the natural course of disease: A higher proportion of people with adenomas in people with a familial risk of CRC compared to people without familial risk of CRC (adjusted OR: 1.75; 95% CI: [1.60; 1.91]) is expected, given the increased risk of CRC in people with a familial risk (relative risk of CRC occurrence: 2.7; 95% CI: [2.3; 3.1] [10]). In terms of a comparable adenoma-carcinoma sequence in people with and without a familial risk of CRC, it can be assumed that an increased risk of CRC is associated with a correspondingly increased risk of adenomas. The higher proportion of people with adenomas observed in people with a familial risk of CRC compared to people without such a risk is consistent with this assumption.

With regard to advanced adenomas , the analysis adjusted for various risk factors did not show any statistically significant differences, but the proportion of people with advanced adenomas in 2 studies was numerically higher in people with a familial risk of CRC than in people without such a risk. Despite the lack of statistical significance in the adjusted analysis, a similar trend

to the proportion of people with adenomas can be seen, meaning that the results regarding advanced adenomas are also compatible with the assumption of a comparable adenoma-carcinoma sequence in people with and without a familial risk of CRC.

A further indirect sign of a comparable adenoma-carcinoma sequence in people with and without a familial risk of CRC is the fact that the proportion of advanced adenomas among all adenomas was similar in people with and without a familial risk of CRC. Since advanced adenomas develop from non-advanced adenomas with a certain probability, this result tends to indicate a comparable adenoma-carcinoma sequence.

The fact that the proportion of people with distal adenomas as well as proximal adenomas was statistically significant (distal adenomas) or numerically higher (proximal adenomas) in people with a familial risk of CRC than in people without such a risk must be analysed in conjunction with the results described above. The higher prevalence of distal and proximal adenomas is consistent with the higher prevalence of any and advanced adenomas in people with a familial risk of CRC. Therefore, these results support the transferability of findings on the natural course of disease.

With regard to the 2 outcomes of adenoma location and tumour stage at CRC diagnosis, the studies included in Henrikson 2015 showed no differences between people with and without a familial risk of CRC - a result that speaks for the transferability of findings on the natural course of disease.

With regard to the location of carcinomas, the data were inconsistent (in 2 studies, distal location of CRC was reported numerically more frequently in people with a familial risk of CRC than in people without such a risk, in 2 studies it was not), so that the results overall do not speak either for or against the transferability of findings on the natural course of disease.

No data were available with regard to other relevant outcomes that describe the natural course of CRC development (see Table 4).

With regard to most of outcomes on the natural course of disease for which data were available from Henrikson 2015, the results suggest the transferability of findings on the natural course of disease. There was a lack of data on key outcomes that describe the course of CRC development - in particular the risk of degeneration, the rate of progression of precancerous lesions, and the symptoms associated with precancerous lesions and carcinomas. The lack of data on these aspects is important for the overall assessment of the natural course of disease: a higher rate of progression in people with a familial risk of CRC would, for example, shorten the preclinical phase[2] in the worst case to such an extent that precancerous lesions and / or

[2] i.e. the phase in which precancerous lesions can be detected and removed; also referred to as sojourn time in the literature

CRC may not be detected in time more often than in people without risk. For this reason, the overall results do not speak either for or against the transferability of findings on the natural course of disease in the general population of at least 50 years of age to people under 50 years of age with a familial risk of CRC.

Table 4: Overview of the results from Henrikson 2015 for the outcomes on the natural course of disease

Outcomes on the natural course of disease	Comparison of people with vs. without a familial risk of CRC			
	Number of underlying studies	Differences in outcome reported	Direction of the respective difference	Relevance with regard to transferability
Precancerous lesions:				
Proportion of people with any adenoma out of all people in each group[a]	2 [20,21]	■	Proportion higher in people with a familial risk of CRC than in people without such a risk	speaks for T.
Proportion of people with distal adenomas out of all people in each group[a]	1 [21]	■	Proportion higher in people with a familial risk of CRC than in people without such a risk	speaks for T.
Proportion of people with proximal adenomas out of all people in each group[a]	1 [21]	■	Proportion higher in people with a familial risk of CRC than in people without such a risk	speaks for T.
Detection rate		-	n. a.	n. a.
Degree of dysplasia: Proportion of people with advanced adenomas out of all people in the respective group[a]	2 [20,21]	■	Proportion of people with advanced adenomas higher in people with a familial risk of CRC than in people without such a risk	speaks for T.
Risk of degeneration	-	-	n. a.	n. a.
Progression speed	-	-	n. a.	n. a.
Precancerous lesions/carcinomas				
Histopathological features	-	-	n. a.	n. a.
Macroscopic features	-	-	n. a.	n. a.
Location of adenomas	1 [21]	□	n. a.	speaks for T.
Location of carcinomas	2 [22,23]	■	Distal location of CRC more common in people with a familial risk of CRC than in people without such a risk	speaks neither for nor against T.
	2 [24,25]	□	n. a.	
Symptoms	-	-	n. a.	n. a.
Carcinomas:				
Tumour stage at CRC diagnosis	3 [23,25,26]	□	n. a.	speaks for T.
Lethality	-	-	n. a.	n. a.

■: In the studies included in Henrikson 2015, there are differences between people with vs. without a familial risk of CRC with regard to the relevant outcome.
□: Studies included in Henrikson 2015 do not indicate differences between people with vs. without a familial risk of CRC with regard to the relevant outcome.
-: No data were available.
a. The proportion of people with any adenomas - or with distal, proximal or advanced adenomas - in all people with a familial risk of CRC or in all people without such a risk was reported.

CRC: colorectal cancer; n. a.: not applicable; T: transferability

4.5 Sub-objective 2c: Studies on the diagnostic accuracy and adverse effects of screening tests in people with a familial risk

For sub-objective 2c, 5 studies were identified (4 studies on diagnostic accuracy, 2 studies on adverse effects of iFOBT and colonoscopy, whereby 1 of the studies contributed data on both diagnostic accuracy and adverse effects of iFOBT and colonoscopy and 1 study presented as supplementary information only contributed data on adverse effects).

4.5.1 Studies on diagnostic accuracy

4.5.1.1 Characteristics of the studies included in the assessment

Four studies on diagnostic accuracy were included [15,19,27,28].

In all included studies, the participants were at least 50 years old. The number of study participants analysed ranged from 373 to 5,643,438. The proportion of people with a familial risk of CRC in these studies ranged from approx. 4% to approx. 45%. A familial risk of CRC was defined in the studies as at least 1 first-degree relative with a CRC diagnosis. In all studies, the age of onset of the disease of the relative(s) was not specified.

The index test in all 4 studies was the iFOBT. The diagnostic accuracy of the colonoscopy was not examined in any of the studies.

With the exception of 1 study (Jung 2020 [18]), the reference standard was colonoscopy. For most studies, it was stated that a histological examination of ablated lesions was performed. However, in the studies in which this was not explicitly stated, this can also be assumed, as the description of the colonoscopies performed indicated compliance with at least minimal quality standards. In contrast to the other studies, the reference standard in Jung 2020 consisted of CRC diagnoses that were made within 1 year of the iFOBT being performed (see detailed description below).

Data on diagnostic accuracy were reported in 2 studies only in relation to the detection of advanced neoplasms, in 1 study only in relation to the detection of CRC and in 1 study in relation to the detection of both target lesions (see

). Advanced neoplasia was defined in all studies as the presence of an adenoma ≥ 1 cm, villous histology, high-grade dysplasia or CRC.

Data on the sensitivity and specificity of the test examined were reported in 3 studies (Cubiella 2014 [16], Jung 2020 and Ng 2013 [19]). In 1 study, only the number of true-negative and false-negative findings was reported, as the analysis referred to people with negative index test results who had undergone a colonoscopy (Cha 2012 study [15]).

Table 5 shows the main characteristics of the included studies on diagnostic accuracy.

Table 5: Characteristics of the studies on diagnostic accuracy included in the assessment

Study	Number of people analysed	People with a familial risk of CRC N (%)	Age of population	Index test	Reference standard	People who were tested using the reference standard	Relevant measures of diagnostic accuracy
Cha 2012	373	30 (8)	≥ 50 Y.	iFOBT	Colonoscopy	Only people with negative iFOBT results	TN & FN
Cubiella 2014	1317	595 (45)	50-69 Y.	iFOBT	Colonoscopy	All	Sensitivity & specificity
Jung 2020	5 643 438	224 178 (4)	50-108 Y.	iFOBT	CRC diagnoses within 1 year	All	Sensitivity & specificity
Ng 2013	4539	572 (13)	50-70 Y.	iFOBT	Colonoscopy	All	Sensitivity & specificity

CRC: colorectal cancer; FN: false-negative findings; iFOBT: immunological faecal occult blood test; N: number of people analysed; TN: true-negative findings; Y.: years

Table 6 shows the criteria used to define advanced neoplasia in the studies on diagnostic accuracy. (The components of the definition are each linked via "or").

Table 6: Definition of advanced neoplasia in the studies on diagnostic accuracy

Study	Components of the definition of advanced neoplasia				
	Adenoma ≥ 1 cm	Villous histology	High grade dysplasia	Sessile serrated lesions	CRC
Cha 2012	x[a]	x	x	-	x
Cubiella 2014	x	x	x	-	x
Ng 2013	x	x	x	-	x[b]

x: Part of the definition of advanced neoplasia.
-: Not part of the definition of advanced neoplasia.
a. Adenomas > 1 cm.
b. In Ng 2013, carcinoma in situ was also counted as advanced neoplasia.
CRC: colorectal cancer

Cubiella 2014

In Cubiella 2014, the diagnostic accuracy of the iFOBT was determined in 1317 people (595 of whom had a familial risk). This was based on a post-hoc analysis of the data from 2 studies (one of which included only people with a familial risk of CRC and one of which included only people without such a risk). The 2 sub-studies were conducted in Spain between 2010 and 2011.

The study included asymptomatic people aged between 50 and 69 years who were scheduled for a colonoscopy. People who had already been diagnosed with CRC or who had undergone a sigmoidoscopy or colonoscopy in the last 3 years, as well as people with hereditary CRC, were excluded. The inclusion criteria were met by 1429 people. 112 of these people were excluded because either no colonoscopy was performed or the faecal test was not sent in, meaning that 1317 people were included in the analysis

Cha 2012

In Cha 2012, the diagnostic accuracy of the iFOBT was determined in 373 people (30 of whom had a familial risk) who had a negative iFOBT result. The study was conducted in Korea from 2009 to 2010.

The study included asymptomatic people aged at least 50 years who decided to undergo a colonoscopy despite negative iFOBT results. People with signs or symptoms that represented a medical indication for a colonoscopy were excluded. No information was provided on the number of people included; only the number of people analysed is known (N= 373).

Jung 2020

In Jung 2020, the diagnostic accuracy of the iFOBT was determined in 5,643,438 people (224,178 of whom had a familial risk). The study was conducted in Korea from 2009 to 2011.

People aged 50 years or older were included. Those who had been diagnosed with cancer or chronic inflammatory bowel disease in the past or who had undergone a colonoscopy in the 180 days prior to the iFOBT were excluded. Of the 6,342,240 people who underwent an iFOBT, 5,643,438 people were included in the analysis (subset of people who met the inclusion criteria and contributed usable data).

The reference standard was a CRC diagnosis made within 1 year of the iFOBT being performed. The CRC diagnoses were taken from a database containing national health insurance data. After a positive iFOBT result in the study, a colonoscopy was performed. In addition to CRC diagnoses made in this way, it can be assumed that the database also contained diagnoses that were made independently of the colonoscopies carried out as part of the study (following a positive iFOBT result) for example, CRC discovered following symptoms. CRC diagnoses were counted as those diagnosed according to ICD-10 (C18-C21, D01.0-D01.3) or the Korean national cancer registration programme. (No further information was provided on the latter).

Ng 2013

In Ng 2013, the diagnostic accuracy of the iFOBT was determined in 4539 people (572 of whom had a familial risk). The study was conducted in China from 2008 to 2012.

The study included asymptomatic people aged between 50 and 70 who had undergone both an iFOBT and a colonoscopy. Excluded subjects included those who had been diagnosed with CRC, colon adenoma, inflammatory bowel disease, hereditary polyposis syndrome or Lynch syndrome in the past, those who had symptoms associated with CRC in the last 6 months and those who had undergone a CRC screening test in the last 5 years.

It was reported that 4539 people had both an iFOBT and a colonoscopy and complete data were available. No information was provided on the number of people originally included. A publication which, according to Ng 2013, describes the recruitment process in more detail (Wong 2010 [29]), indicated that the study participants included in Ng 2013 were probably people who decided to have a colonoscopy after initially undergoing an iFOBT as part of a screening programme. Approximately 50% of the 3430 study participants in Wong 2010 additionally opted for a colonoscopy after an initial iFOBT. (However, it is not certain to what extent Ng 2013 and Wong 2010 were overlapping cohorts; the study population in Wong 2010 consisted of 3430 study participants recruited from May 2008 to December 2009).

In addition, in Ng 2013, the results were reported separately only for advanced adenomas and CRC, so that to determine the number of people with advanced neoplasms, the number of people with advanced adenomas (referred to as "advanced neoplasm" in Ng 2013) and the number of people with CRC had to be added.

The Wong 2015 publication was also identified in the literature screening. Information in the publications indicated that there were overlapping study populations. In the present assessment, the results from the publication Ng 2013 were used (among other things, because in Wong 2015 sensitivity and specificity were reported over several consecutive screening rounds [with an unclear screening process], while in Ng 2013 data on the 2x2 table were available for a single screening).

4.5.1.2 Overview of the target lesions examined

Table 7 provides an overview of the target lesions relevant for the present assessment for which results are available from the included studies on the diagnostic accuracy of the iFOBT. No data were available on the diagnostic accuracy of colonoscopy.

Table 7: Overview of the relevant target lesions for which results were reported in the diagnostic accuracy studies

Study	Target lesions	
	Advanced neoplasia	CRC
Cha 2012	●	-
Cubiella 2014	●	-
Jung 2020	-	●
Ng 2013	●	●

●: Data reported and usable.
-: No data collected for this target lesion.
CRC: colorectal cancer

4.5.1.3 Results of the studies on diagnostic accuracy

4.5.1.3.1 Advanced neoplasia

Data on the diagnostic accuracy regarding the detection of advanced neoplasia were available from 3 studies (Cha 2012, Cubiella 2014, Ng 2013). Only 2 of these studies (Cubiella 2014 and Ng 2013) reported data on the sensitivity and specificity of the index test. In both studies, the diagnostic accuracy of the iFOBT was investigated and colonoscopy was the reference standard. Both studies combined had a total sample size of 5856 people (1167 of whom had a familial risk of CRC).

In a bivariate meta-analysis of the sensitivity and specificity of the iFOBT with the data from these 2 studies, the sensitivity and specificity of the iFOBT were of a similar order of magnitude in relation to the point estimate for people with and without a familial risk of CRC: The pooled estimate showed a sensitivity of 36.3% (95% CI: [27.5; 46.0]) in people without familial risk of CRC compared with 38.1% (95% CI: [29.3; 47.7]) in people with such a risk. The specificity in the pooled estimate was 94.1% (95% CI: [88.5; 97.1]) in people without a familial risk of CRC compared with 95.7% (95% CI: [88.7; 98.4]) in people with such a risk.

From the Cha 2012 study, only data on true and false-negative findings and the negative predictive value derived from them were available. These data were not used for the present assessment, as data on sensitivity and specificity were available from other studies.

Summarized assessment with regard to the detection of advanced neoplasia

In the overall assessment of the results on diagnostic accuracy with regard to the detection of advanced neoplasia, the result of the bivariate meta-analysis based on the data from Cubiella 2014 and Ng 2013 is the most informative. Compared with the results of the Cha 2012 study, these 2 studies do not exhibit the aspects that limit the informative value of the other studies:

Cha 2012 was the smallest study with 373 people analysed (only 30 of whom had a familial risk). In comparison, the analysis with data from Cubiella 2014 and Ng 2013 showed a total sample size of 5856 people (1167 of whom had a familial risk of CRC).

In Cha 2012, only some of the people tested with the index text received the reference standard: complete results for the 2x2 table, which would be necessary for an adequate evaluation of the diagnostic accuracy of the index tests in the comparison between people with and without a familial risk, were therefore missing.

The meta-analytical summary of the data from Cubiella 2014 and Ng 2013 showed a comparably high sensitivity and specificity of the iFOBT between people with and without a familial risk of CRC. Overall, the results of the identified studies on diagnostic accuracy therefore suggest that people with a familial risk of CRC are comparable to people without such a risk with regard to the detection of advanced neoplasia using iFOBT.

4.5.1.3.2 CRC

Data on the diagnostic accuracy regarding the detection of CRC was available from 2 studies (Jung 2020 and Ng 2013). Only the results from 1 of these studies were used to assess transferability (Jung 2020).

In Ng 2013, the results on the sensitivity of the iFOBT are not sufficiently informative due to the very low number of people diagnosed with CRC using the reference standard. (Only 18 people without a familial risk of CRC and 4 people with such a risk were diagnosed with CRC). This results in very wide CIs for the sensitivity; the specificity is estimated at 89.3% (95% CI: [88.3; 90.3]) for people without a familial risk of CRC and 89.8% (95% CI: [86.9; 92.1]) for people with such a risk.

In Jung 2020, the sensitivity and specificity of the iFOBT were similar between people with and without a familial risk of CRC, both in terms of the point estimate and taking into account the 95% CI: the sensitivity was 64.1% (95% CI: [63.4; 64.9]) in people without a familial risk of CRC compared with 64.4% (95% CI: [61.2; 67.6]) in people with such a risk. The specificity was 94.3% (95% CI: [94.2; 94.3]) in people without a familial risk of CRC compared to 93.8% (95% CI: [93.7; 93.9]) in people with such a risk.

Summarized assessment with regard to detection of CRC

An imperfect reference standard was used in Jung 2020: as not all study participants underwent a colonoscopy, it can be assumed that some of the lesions present at the time the iFOBT was performed were overlooked. The CRC diagnoses made during the follow-up consisted of diagnoses made after an initially positive iFOBT result and diagnoses made during the course of 1 year due to other reasons (e.g. a colonoscopy to clarify symptoms). The

diagnostic accuracy reported in Jung 2020 therefore does not capture the ability to detect all CRCs, but rather the ability to detect those CRCs that caused symptoms within 1 year.

Even if the reference standard in Jung 2020 was imperfect, the 1-year examination phase should be viewed positively: such a procedure would be part of the ideal reference standard, which would include an initial colonoscopy in all study participants with a sufficiently long follow-up.

Overall, the results from Jung 2020 indicate that the sensitivity and specificity of the iFOBT with regard to the detection of CRC that become clinically apparent within 1 year are comparable between people with and without a familial risk of CRC.

4.5.1.3.3 Summarized assessment of all studies on diagnostic accuracy

With regard to the detection of advanced neoplasia, the meta-analytical summary of the results of 2 studies showed a comparably high sensitivity and specificity of the iFOBT between people with and without a familial risk of CRC. The data from the third study on this aspect were not used for the present assessment, as it did not provide complete data on the 2x2 table and the informative value of its results is therefore limited. With regard to the detection of CRC, the results of 1 very large study showed a comparably high sensitivity and specificity of the iFOBT for people with and without a familial risk of CRC. In the second study on this aspect, the informative value of the results was limited due to an insufficient number of people with an event. Overall, the results of the studies on diagnostic accuracy therefore support the transferability of findings on the diagnostic accuracy of the iFOBT in the general population to people with a familial risk of CRC. The diagnostic accuracy of colonoscopy remained unclear.

4.5.2 Studies on the adverse effects of screening tests

4.5.2.1 Characteristics of the studies included in the assessment

One study on adverse effects of colonoscopy (Hilsden 2015 [17]) and one study on adverse effects of iFOBT and / or colonoscopy (Ng 2013 [19]) were identified. Hilsden 2015 did not meet the inclusion criteria for sub-objective 2c (as no results on diagnostic accuracy were reported); however, the results of this study were used as supplementary information, as it provided information on the adverse effects of colonoscopy.

Hilsden 2015

In the study Hilsden 2015, 18,456 people (including 10,027 with a familial risk of CRC) underwent a colonoscopy for screening for CRC. People with a familial risk of CRC were described in the study publication as having a family history of CRC or colorectal polyps (no further details). This was a retrospective cohort study conducted in Canada between January 2008 and December 2010.

People between the ages of 40 and 74 were included. The average age of the study population is not reported in the study publication, but states that 16% of the study population fell into the age group 40 to 50 years, 72% into the age group 50 to 65 years and 12% into the age group 65 to 74 years. People who had previously had a positive iFOBT result or who had undergone a colonoscopy for surveillance after polypectomy were excluded.

Results on colonoscopy-related adverse events and colonoscopy-related deaths were reported for the two groups of people with and without a familial risk of CRC. The results for these outcomes were based on data on emergency department visits and hospital admissions obtained from the Canadian Institute for Health Information database.

Colonoscopy-related adverse events were counted as emergency department visits or hospitalizations that occurred within 30 days of the colonoscopy and for which it was either documented that the people' decision to visit an emergency department was likely influenced by the previous colonoscopy, or which were classified by the study investigators as being clearly caused by the colonoscopy. Which of the visits had a causal link to the colonoscopy was determined by reviewing the respective patient records; a subset (perforations, cardiac events and questionable cases) were additionally assessed by gastroenterologists.

Ng 2013

As the study contributed data on the diagnostic accuracy of the iFOBT, it has already been described in detail in Section 4.5.1.1.

Ng 2013 contains information on screening test-related serious adverse events, but not on the type of data collection and the operationalization of this outcome. Only perforations and bleeding were mentioned as examples of events that are included in the category of serious adverse events.

4.5.2.2 Overview of the adverse effects investigated

Table 8 provides an overview of the adverse event categories for which results are available from the included studies.

Table 8: Overview of studies with results on adverse events of screening tests

Study	Outcomes		
	Screening test-related[a] serious adverse events	Colonoscopy-related adverse events	Colonoscopy-related deaths
Hilsden 2015[b]	-	●	●
Ng 2013	●	-	-

●: Data reported and usable.
-: No data reported (no further details) / outcome not recorded.
a. iFOBT and colonoscopy
b. Study did not meet the inclusion criteria, but was used as supplementary information for sub-objective 2c to assess the adverse effects of screening tests.

iFOBT: immunological faecal occult blood test

4.5.2.3 Results of the studies on adverse effects of the screening tests

In Hilsden 2015, colonoscopy-related adverse events were reported in 0.56% of people without a familial risk of CRC and in 0.72% of people with such a risk; this difference was not statistically significant (no confounder control). It was not specified which specific colonoscopy-related adverse events occurred in which frequency in people with and without a familial risk of CRC. In the overall group, bleeding after polypectomy was reported most frequently (54 people) followed by gastrointestinal symptoms (mainly abdominal pain) in 36 people.

No colonoscopy-related deaths were reported in either group.

In Ng 2013, no screening test-related serious adverse events were reported in either people without a familial risk of CRC or in people with such a risk.

Summarized assessment

In Ng 2013, no information was provided on the type of data collection for the outcome of screening test-related serious adverse events. It can therefore be assumed that serious adverse events were not fully recorded.

In Hilsden 2015, colonoscopy-related adverse events and colonoscopy-related deaths represent only a subset of all adverse events or deaths. The classification as colonoscopy-related was also the result of a subjective evaluation by the study authors, which makes the results susceptible to bias.

Although not all adverse events or deaths were recorded in both studies, this does not call into question the informative value of the results in the context of the present assessment: although underreporting of adverse events is possible in both studies, no different underreporting is to be expected for people with and without a familial risk of CRC. In addition,

the comparison reported by Hilsden 2015 (0.72% versus 0.56%) was not controlled for possible confounders, meaning that any difference in the frequency of adverse events could also be attributed to other factors, such as differences in the average age of the groups or differences in the invasiveness of colonoscopy (more frequent biopsies in people with a familial risk of CRC). In the overall assessment of the results on adverse effects of iFOBT and colonoscopy, the data do not indicate a (relevant) higher risk of iFOBT and colonoscopy in people with a familial risk of CRC than in people without such a risk. The results therefore support the transferability of findings on the adverse effects of iFOBT and colonoscopy in the general population to people with a familial risk of CRC.

4.6 Sub-objective 2d: Studies on CRC treatment in people with a familial risk

No relevant study was identified for sub-objective 2d.

5 Summarized assessment

Sub-objective 1: Assessment of the benefits and harms of CRC screening in people under 50 years of age with a familial risk of CRC on the basis of comparative intervention studies

No comparative intervention study of the screening chain in people under 50 years of age with a familial risk was identified, so that no assessment of the benefits and harms of CRC screening based on such studies was possible. Therefore, studies were sought that would allow conclusions to be drawn on the transferability of findings on CRC screening in people without a familial risk of CRC or people aged 50 years and older with a familial risk to people younger than 50 with a familial risk.

Sub-objective 2a: Effects of CRC screening in comparative intervention studies of the screening chain in people aged at least 50 years with a familial risk of CRC

A randomized intervention study of the screening chain of people with and without a familial risk of CRC of at least 55 years of age was included. There were no differences in effects between people with and without a familial risk of CRC in the study population. However, when considering the other transferability aspects (sub-objectives 2b to 2d), there was no evidence to show that results from people aged at least 55 years are transferable to people under 55 years. The evidence for sub-objective 2a therefore speaks neither for nor against the transferability of findings on CRC screening in people aged at least 50 years who are not known to have a familial risk of CRC to people under 50 years with a familial risk.

Based on the results of the PLCO trial, due to a lack of data, the extent to which overdiagnosis could occur in people under the age of 50 with a familial risk also remains unclear.

Sub-objective 2b: Natural course of CRC

A systematic review was included which, on the basis of 7 studies relevant to the present assessment, enabled a comparison between people with and without a familial risk of CRC with regard to several outcomes describing the natural course of disease. With the exception of the tumour location, the results for these outcomes supported the transferability of findings on the natural course of disease. However, there were other outcomes that were of particular importance for the assessment of the natural course of disease (such as rate of progression), for which no data were available. The evidence for sub-objective 2b therefore speaks overall neither for nor against the transferability of findings on the natural course of disease.

Sub-objective 2c: Diagnostic accuracy and direct (adverse) effects of the established screening tests

Four studies with data on the diagnostic accuracy of the immunological faecal test were included. The results of 3 of these studies indicate that the sensitivity and specificity of this

test with regard to the detection of advanced neoplasia (2 studies) and the detection of CRC (1 study) are comparable between people with and without a familial risk of CRC. This supports the transferability of findings on the diagnostic accuracy of the established screening tests. No complete data on the diagnostic accuracy (sensitivity and specificity) were available for the other studies.

We included 1 study with data on adverse effects of the immunological faecal test and colonoscopy and considered 1 study with data on adverse effects of colonoscopy as supplementary information. The data from these studies do not indicate a (relevant) higher risk of the immunological faecal test and colonoscopy in people with a familial risk of CRC compared to people without such a risk - in this respect, they support the transferability of findings on adverse effects of the immunological faecal test and colonoscopy.

For sub-objective 2c, against the background of the results on diagnostic accuracy, it is assumed overall that the evidence supports the transferability of findings on diagnostic accuracy and adverse effects of the established screening tests.

Sub-objective 2d: CRC treatment for people with a familial risk of CRC

No study on CRC treatment in people with a familial risk was identified. The question of the transferability of findings on CRC treatment therefore remains open for sub-objective 2d.

Overview of the conclusions on transferability for sub-objectives 2a to 2d

Table 9 shows the conclusions on transferability for each of the transferability aspects.

Table 9: Overview of the conclusions on transferability per sub-objective

Subgoal **Partial aspect**	**Summarized assessment of transferability per sub-objective**
Sub-objective 2a: Effects of CRC screening in people aged at least 50 with a familial risk	Evidence speaks neither for nor against transferability
Sub-objective 2b: Natural course of CRC in people with a familial risk	Evidence speaks neither for nor against transferability
Sub-objective 2c: Diagnostic accuracy and direct (adverse) effects of established screening tests in people with a familial risk	Overall, evidence speaks for transferability
Diagnostic accuracy of screening tests	Evidence speaks for transferability
Adverse effects of screening tests	Evidence speaks for transferability
Sub-objective 2d: CRC treatment in people with a familial risk of CRC	No study identified
CRC: colorectal cancer	

Overall conclusion on transferability

The results only support transferability with regard to diagnostic accuracy and the direct adverse effects of the established screening tests. This was not the case for the other aspects of transferability. Therefore, based on the evidence identified, it remains unclear overall whether findings on CRC screening in people aged 50 years or older who are not known to have a familial risk of CRC are transferable to people under 50 years of age with a familial risk.

6 Classification of the assessment result

Important knowledge gaps in the assessment of transferability

In the transferability assessment, the question was whether the benefit-harm ratio of CRC screening in the general population of at least 50 years of age is transferable to people under 50 years of age with a familial risk. On the basis of the present assessment, it remains open whether this benefit-harm ratio is more or less favourable than in the general population or whether it is comparable. In the following, those knowledge gaps regarding the 4 aspects of transferability (sub-objectives 2a to 2d) that are of particular relevance for the overarching assessment of transferability are identified. For the knowledge gaps, hypothetical scenarios are presented that imply a less favourable benefit-harm ratio of CRC screening in people under 50 years of age with a familial risk and would therefore argue against transferability.

Knowledge gap: Rate of progression of precancerous lesions (sub-objective 2b)

There are different hypotheses regarding the natural course of CRC, which can generally be assigned to 1 of 2 assumptions regarding the adenoma-carcinoma sequence: According to one hypothesis (also referred to in the literature as the "polyp age shift" hypothesis [30]), adenomas develop at a younger age in people with a familial risk of CRC, so that for a given age, more adenomas are present in people with a familial risk of CRC compared to people without such a risk (with a comparable risk of adenoma and degeneration). According to an alternative hypothesis (also referred to in the literature as the "aggressive polyp" hypothesis [30]), people with a familial risk of CRC have a higher risk of degeneration and possibly a higher rate of adenoma progression compared to people without such a risk (with a comparable adenoma risk). It remains unclear which of the two hypotheses more accurately describes the adenoma-carcinoma sequence in people with a familial risk: the data compiled in the present assessment also leave this question unanswered.

The rate of progression of precancerous lesions in people with a familial risk of CRC compared to people without such a risk is important for the assessment of transferability. This is because a higher rate of progression in people with a familial risk of CRC could change the benefit-harm ratio of CRC screening in people under 50 years of age with a familial risk compared to the general population:

- If precancerous lesions were to develop into CRC considerably faster in people with a familial risk of CRC than in people without such a risk, this would shorten the preclinical phase (i.e. the period in which precancerous lesions can be detected and removed [sojourn time]). Using the screening intervals of the existing CRC screening in Germany, a higher proportion of precancerous lesions in people with a familial risk of CRC could therefore not be detected in time. As a result, more CRCs would be detected at late stages (with a correspondingly poorer prognosis) compared to people without a familial

risk. Such a scenario would reduce the effect of CRC screening in the general population (e.g. in terms of CRC incidence) in people under 50 years of age with a familial risk.

- Faster progression could be taken into account by shorter screening intervals, and earlier development of precancerous lesions by starting CRC screening earlier. If the screening interval is shortened for people with a familial risk of CRC and / or CRC screening starts at a younger age, it is to be expected that this would result in more frequent colonoscopies overall and thus more adverse events. Such a scenario would therefore increase the harm of CRC screening in people under the age of 50 with a familial risk compared to the general population.

A higher rate of progression could therefore - both with and without adjustment of the screening interval and the lower age limit - result in the benefit-harm ratio of CRC screening being less favourable in people with a familial risk of CRC than in the general population.

With regard to the detection of CRC, the Jung 2020 study [18] provided results on the diagnostic accuracy of the iFOBT with regard to the detection of CRC that become clinically conspicuous within 1 year (for a description of the study, see Section 4.5.1.1). In Jung 2020, comparative results were reported on the proportion of interval cancers (defined as the proportion of false-negative findings among all negative findings on iFOBT). The proportion of interval cancers was reported to be higher for people with a familial risk of CRC compared to people without such a risk. In Jung 2020, a higher rate of progression in people with a familial risk of CRC is presented as a possible explanation for this. However, the proportion of interval cancers reported in Jung 2020 depends on the frequency of CRC diagnoses in the subgroups with and without a familial risk that are made within 1 year. Since a higher proportion of CRC diagnoses is to be expected in people with a familial risk of CRC than in people without such a risk, these results are not necessarily due to a higher risk of degeneration and / or a faster rate of progression. Overall, neither the data from Jung 2020 nor the evidence identified for sub-objective 2b can provide information on the rate of progression of precancerous lesions in people with a familial risk of CRC.

Knowledge gap: symptoms associated with precancerous lesions and carcinomas (sub-objective 2b)

It is unknown whether and with regard to which characteristics (including type, frequency, intensity, duration, time of occurrence) the symptoms associated with precancerous lesions and carcinomas differ between people with a familial risk of CRC and those without such a risk. More frequent, more pronounced or earlier onset of symptoms in people with a familial risk of CRC than in people without such a risk could increase the likelihood of an (earlier) visit to the doctor to clarify the symptoms and thus reduce the effect of CRC screening in the general population in people under 50 years of age with a familial risk. Nevertheless, a recent Canadian study of people with "early-onset" CRC (i.e. people diagnosed with CRC before the

age of 50 without a positive family history) shows that they had more symptoms at the time of diagnosis and that the interval between symptom onset and CRC diagnosis was longer than in people diagnosed with CRC after the age of 50 [31]. The authors of the study associate this finding with poorer symptom awareness at a younger age; however, it remains unclear whether this finding is transferable to people with a familial risk of CRC under the age of 50, as CRC diagnosed in younger people is only partially associated with a familial risk of CRC [32] and knowledge of a familial risk of CRC could increase symptom awareness.

Knowledge gap: Diagnostic accuracy of colonoscopy (sub-objective 2c)

The study data available for sub-objective 2c refer to the diagnostic accuracy of iFOBT with colonoscopy as the reference test; the diagnostic accuracy of colonoscopy in people with a familial risk of CRC versus those without such a risk remains unclear. A poorer diagnostic accuracy of colonoscopy in people with a familial risk of CRC would reduce the effect of CRC screening in the general population of people under 50 years of age with a familial risk. Studies investigating the diagnostic accuracy of colonoscopy would be feasible. In these studies, a sufficiently long and complete follow-up could be used as a reference standard: A different proportion of interval carcinomas in people with and without a familial risk could be an indication of a different diagnostic accuracy of colonoscopy.

Knowledge gap: CRC treatment in people with a familial risk of CRC (sub-objective 2d)

Due to a lack of data, it remains unclear whether there are differences in the benefit of CRC treatment between people with a familial risk of CRC and people without such a risk. Depending on whether a situation with or without organized CRC screening is assumed for people under 50 years of age with a familial risk, different consequences arise: In a situation in which CRC screening is assumed in people under 50 years of age with a familial risk (i.e. in which CRC was detected via screening), potentially worse treatment outcomes in people with a familial risk of CRC than in people without such a risk would reduce the effect of CRC screening in people with a familial risk of CRC. In a situation without CRC screening in people with a familial risk of CRC (e.g. where CRC was detected and treated based on symptoms), better treatment outcomes in people with a familial risk of CRC would possibly reduce the effect. The meta-analysis of 17 cohort studies with people with CRC in the systematic review by Li et al. of 2022 [33] shows that different treatment outcomes are conceivable for people with and without a familial risk: Overall survival was found to be better in people with a familial risk of CRC than in people without such a risk, although there was a high degree of heterogeneity and the effect of a positive family history was not statistically significant, depending on the definition of familial risk.

Differences in treatment outcomes between people with and without a familial risk may be due to differences in genetic characteristics of CRC. As there were no data on tumour genetics

in people with a familial risk of CRC, the risk of different treatment outcomes due to genetic differences cannot be assessed.

Knowledge gap: Age of people with a familial risk of CRC (all sub-objectives)

For all included studies - with the exception of Hilsden 2015, which looked at people aged 40 and over - only people aged 50 and over were included, meaning that these studies do not represent the target population for this assessment, at least in terms of age. Hilsden 2015 provided findings on the occurrence of colonoscopy-related adverse events and deaths. As only 16% of the study population were in the age group 40 to 50 years (see Section 4.5.2.1), the results from this study are not necessarily representative of the target population of this assessment. The results of the included studies that support transferability therefore initially only support transferability of findings on CRC screening in people from the general population of at least 50 years of age to people of at least 50 years of age with a familial risk of CRC. It remains to be seen whether the postulated transferability also applies to people under the age of 50.

Table 10 contains an overview of the aspects described above for which there is no evidence and which are of particular relevance for the assessment of transferability.

Table 10: Overview of knowledge gaps of particular relevance for the assessment of transferability

Aspects	Hypothetical scenario that would argue against transferability
Sub-objective 2b: Natural course of CRC in people with a familial risk	
Rate of progression of precancerous lesions	▪ Faster progression of precancerous lesions in people with a familial risk of CRC than in people without such a risk, so that the preclinical phase is short and precancerous lesions cannot be detected in time (consequence: despite screening, people with a familial risk of CRC are diagnosed with higher-stage CRC or CRC with a poorer prognosis than people without such a risk)
Symptoms associated with precancerous lesions and carcinomas	▪ In people with a familial risk of CRC, symptoms occur more frequently, more clearly or earlier than in people without such a risk. ▪ People with a familial risk of CRC are better able to recognize symptoms than people without such a risk.
Sub-objective 2c: Diagnostic accuracy and direct (adverse) effects of established screening tests in people with a familial risk	
Diagnostic accuracy of colonoscopy	▪ Lower diagnostic accuracy (especially sensitivity) of colonoscopy, especially with regard to the detection of precancerous lesions in people with a familial risk of CRC compared to people without such a risk
Sub-objective 2d: CRC treatment in people with a familial risk of CRC	
CRC treatment for people with a familial risk of CRC	▪ Poorer treatment outcomes with regard to CRC detected in screening in people with a familial risk of CRC than in people without such a risk or ▪ Better treatment outcomes for clinically (i.e. not via screening) detected CRC in people with a familial risk of CRC than in people without such a risk
Sub-objectives 2a to 2d	
Age of people with a familial risk of CRC	▪ Results on transferability postulated for people of at least 50 years of age with a familial risk of CRC do not apply to people younger than 50 with a familial risk
CRC: colorectal cancer	

Evaluation of the FARKOR study

Description of the FARKOR study

The present assessment should be seen in the context of the results of the FARKOR (screening for familial risk of CRC) study [34-36]. The FARKOR study is a pilot project funded by the Federal Joint Committee's (G-BA's) Innovation Fund, the results of which prompted a review of the directive on organized cancer screening programmes and the directive on screening for cancer to determine whether there was a need for revision (see the decision of the Innovation Committee at the G-BA in accordance with §92b (3) Social Code Book (SGB) V on the completed FARKOR project [37]). As part of this pilot project, between October 2018 and March 2021, people aged 25 to under 50 in Bavaria were examined for the presence of a familial risk of CRC. Among others, people with FAP or chronic inflammatory bowel disease or people who were undergoing follow-up care after being treated for CRC were excluded. The people recruited were members of several statutory health insurance funds in Bavaria. The

majority of participants were recruited by their doctors (91% of participants were recruited in this way). The participating doctors took a simple family history from all participants (questions about first or second degree relatives with CRC), while a smaller proportion of participants were also asked a more detailed family history, including questions about hereditary CRC in the family. If the family history was positive, the participants decided after a medical consultation either to undergo an iFOBT, a colonoscopy or no screening measure. People with a positive iFOBT were offered a colonoscopy. The study was described in the evaluation report as a prospective population-based observational study [35]. Part of the FARKOR project was also a health economic evaluation using a decision analytic model (Markov model) [36,38].

The FARKOR observational study was not included in the present assessment because it was not a comparative intervention study and no genuine data were reported on a comparison of people with and without a familial risk of CRC (the evaluation report used routine data for a comparative analysis of the distribution of precursor lesions [35]).

While the present assessment mainly included studies with people aged 50 years or older, the results from the FARKOR study referred to people under 50 years of age with a familial risk of CRC and thus to the target population of the present assessment. For this reason, a comparison is appropriate with regard to those outcomes that were considered both in the FARKOR study and in the present assessment. In addition to a process evaluation, in which, among other things, the willingness to participate was examined, the FARKOR study recorded several outcomes among the participants that were also considered in the present assessment [35]. A comparison between the results of the present assessment and the FARKOR study is possible for the prevalence of adenomas, advanced adenomas and CRC as well as for colonoscopy complications.

Prevalence of adenomas, advanced adenomas and CRC

A simple family history was taken from 25,847 people. In 5769 people, indications of first- or second-degree relatives with CRC were identified - this corresponds to 22.3% of all people for whom a simple family history was taken. Of the 5769 people with a positive family history, 1188 underwent an iFOBT and 1595 had a colonoscopy. In total, adenomas were detected in 287 people (17.2% of all people who had a colonoscopy), including serrated adenomas in 89 people, tubular adenomas in 173 people and tubulovillous adenomas in 26 people. Polyps were detected in 166 people (10.4%), including hyperplastic polyps in 140 people, advanced adenomas in 76 people (4.8%), and CRC in 4 people (0.3%) [35]. In 278 people who underwent colonoscopy as part of the FARKOR study, a colonoscopy had already been performed in the last 5 years. If only those people who had not had a colonoscopy in the last 5 years are considered (i.e. 1317 people who had a colonoscopy as part of the FARKOR study), adenomas were found in 232 people (17.6%), polyps in 132 people (10.0%), advanced adenomas in 78

people (5.9%) and CRC in 4 people (0.3%) [34]. In comparison, in the Wark 2009 study considered in Section 4.4 (one of the primary studies included in Henrikson 2015), 15.8% of people with a positive family history (1 first-degree relative with CRC) had adenomas and 7.7% had advanced adenomas. The data on the proportion of people with advanced adenomas among people with all adenomas was comparable between Wark 2009 and the FARKOR study. With regard to this outcome, there are thus indications of comparable correlations in people over and under the age of 50 with a familial risk of CRC.

Colonoscopy complications

In the FARKOR study, complications were reported in 4 colonoscopy patients (0.25% of those who underwent colonoscopy). Bleeding was reported in 3 of these people (in 1 person the exact complication was unclear). None of the 4 complications required surgical treatment [35]. In comparison, in the Hilsden 2015 study, colonoscopy-related adverse events were reported in 0.72% of people with a familial risk of CRC (presumably the majority of these were bleeding; see Section 4.5.2.3). There was also a comparable frequency of colonoscopy-related adverse events and complications between people over and under the age of 50 with a familial risk of CRC.

The FARKOR modelling study

Modelling is a simplified representation of reality and as such is based on more or less reliable assumptions. Modelling can be used to investigate how benefits and harms relate to each other, and in which direction and in which magnitude benefits and harms shift when certain variables (e.g. the screening interval) are changed. The effects of uncertainties in the model parameters (e.g. the prevalence data included) should also be examined in the context of modelling studies (e.g. [39,40]). However, modelling is only partially based on empirical data and cannot be considered empirical evidence, so that results from modelling have at best a very low certainty of results. For this reason, modelling studies were not included in sub-objective 1. Under certain conditions, however, modelling studies can support the derivation of the evidence base.

In modelling studies, assumptions must be made about a number of aspects of CRC screening - including the aspects that were the subject of this assessment. Ideally, data from clinical studies can be used to make the assumptions more or less plausible, depending on the certainty of conclusions of the studies. Modelling studies must, for example, work with assumptions regarding the natural course of CRC in people with a familial risk of CRC that lack supporting data. The "polyp age shift" hypothesis is often assumed [30,36,41-45], whereby the age-specific incidence of adenomas and CRC in the general population is multiplied by a given factor (see e.g. [41]).

In the FARKOR modelling study, the underlying progression probabilities for the transition from the health state “healthy” to non-advanced adenomas and from non-advanced to advanced adenomas were adjusted using the age- and gender-specific frequencies from the FARKOR study. However, for the progression from advanced adenomas to CRC, the age- and sex-specific CRC incidence in the general population - adjusted for the increased relative CRC risk in people with a familial risk of CRC - was used for model calibration [36,38].

Since the modelling based on the data of the FARKOR study - like the FARKOR observational study itself - only examines the group of people under 50 with a familial risk of CRC, it does not allow any conclusions to be drawn about the transferability of findings on CRC screening in the general population of at least 50 years of age to people under 50 with a familial risk of CRC: for this reason alone, it was not included in the assessment.

The modelling on which the CRC screening recommendations of the U.S. Preventive Services Task Force were based and in which CRC screening from the age of 45 was also considered, does not take into account any specifics of people with a familial risk of CRC because the analysis refers to the general population [46,47].

Outlook

The particularly relevant knowledge gaps identified above indicate those aspects for which meaningful data would have to be available in order to be able to assume transferability. If suitable data are available to clarify the open questions - particularly with regard to the relevant knowledge gaps - it could be assumed that the findings on CRC screening in the general population are transferable.

This is particularly relevant as no ongoing studies on the screening chain were identified that are expected to provide results on the benefits and harms of CRC screening in people under 50 years of age with a familial risk of CRC. With regard to the ongoing study on the screening chain described in Section A3.1.5 of the full report [48], it remains unclear whether the study has been continued and whether results are expected to be published in the foreseeable future. With regard to the potentially relevant Nordic-European-Initiative-on-Colorectal-Cancer (NordICC) study - a randomized study of the screening chain with 84,585 study participants - no relevant results are to be expected, as, according to the study protocol, the family history was apparently only (completely) recorded in the intervention arm [49].

Accompanying assessment for the expansion of CRC screening

As it is unlikely that there will be any meaningful studies in the near future that will allow conclusions to be drawn about the benefits and harms of CRC screening in people under 50 with a familial risk of CRC, an accompanying assessment should be carried out if CRC screening is introduced in this group of people. An accompanying assessment was suggested by 2

persons submitting comments during the hearing on the preliminary report. The topic was also discussed in the oral debate on the preliminary report.

An accompanying assessment should be carried out in such a way that it allows conclusions to be drawn about the benefits and harms of CRC screening in people under the age of 50 with a familial risk of CRC.

A basic prerequisite for reliable conclusions on the advantages and disadvantages of an intervention is a comparison. The optimal methodological approach would be a (cluster) RCT within Germany, which could be designed as a regional comparison, e.g. by comparing model regions in which CRC screening is introduced with the remaining regions (in which no risk group screening is introduced). A corresponding non-RCT would also be conceivable, even if this would be associated with a lower certainty of results. However, the following problem of such a study was pointed out in the oral debate: In view of the guideline recommendation for CRC screening in people under 50 years of age with a familial risk of CRC (recommendation of a screening colonoscopy for first-degree relatives of people with CRC 10 years before the age of first manifestation of the diseased relative(s) and at the latest from the age of 40 to 45 years [7]), in the opinion of the persons submitting comments, it would have to be expected that CRC screening would also be carried out within the control group to a not insignificant extent ("contamination" of the control group through "grey screening").

For this reason, further options for a comparative study on the benefits and harms of CRC screening were discussed in the oral debate. An alternative option for generating a concurrent control group could be to compare the situation in Germany after the introduction of CRC screening in people under 50 with a familial risk of CRC with the situation in a country in which no comparable risk group screening is carried out and which is approximately comparable to Germany in terms of population structure and medical standards. In the discussion, Sweden was cited as a potentially suitable country for such a comparison. In Sweden, an organized CRC screening programme for people between 60 and 74 years of age was introduced nationwide in 2022 [50]; organized CRC screening for people under 50 years of age with a familial risk of CRC does not appear to exist at present. However, prior to the decision for such an assessment, it would have to be examined whether opportunistic CRC screening in people with a familial risk of CRC takes place in Sweden (or in the country intended as a control group), similar to Germany. In addition, comprehensive data differentiated by family history are available for Sweden for all CRC cases reported to the Swedish Cancer Registry. This is due to the possibility of linking data from the Swedish Multi-Generation Registry, which includes data on family relationships for all people born in Sweden after 1931 or registered in Sweden after 1960 [51], with data from the Swedish Cancer Registry, which documents all reported cancer diagnoses in Sweden and has existed since 1958 [52]. This opens up the possibility of investigating the occurrence of CRC specifically for people under the age of 50 with a familial

risk of CRC. The data collection was used, among other things, to investigate the familial increased risk of CRC depending on the degree of relationship [53-55]. By linking the data with data on deaths - as was done in the aforementioned studies [53-55] - it would also be possible to investigate mortality.

A comparison of people under 50 years of age with a familial risk of CRC in Germany (intervention group with the introduction of risk group screening) with a control group in which no organized risk group screening takes place (e.g. Sweden) with regard to patient-relevant outcomes would offer the possibility of approaching a conclusion on the benefits and harms of CRC screening in this group of people on the basis of a prospective non-randomized controlled study with a concurrent control group.

A study protocol should define the key points of the accompanying assessment. The assessment should relate to patient-relevant outcomes (see e.g. Section A.2.1.3 of the full report). Care should be taken to ensure that at least those patient-relevant outcomes are recorded for Germany for which data are available for the control group (if the Swedish registry data were to be used, at least the CRC incidence should be recorded). In addition, harms resulting directly and indirectly from the test used for CRC screening or from subsequent diagnostic examinations (e.g. complications of colonoscopy) should be recorded. The recording of relevant confounders and subsequent adjustment for these variables in the data analysis would be essential for the informative value of the results (in Sweden, linking the data from the Multi-Generation Registry and Cancer Registry with census data [see [53-55]] may enable adjustment for other confounders in addition to age and gender). The data collection in Germany should cover all relevant confounders and include both patient-related confounders and those related to medical care. The follow-up period, data analysis and criteria for deciding on the success or failure of CRC screening in people under 50 with a familial risk of CRC should also be pre-specified; this includes the definition of a primary outcome to investigate the patient-relevant benefit.

The introduction of CRC screening in people under the age of 50 with a familial risk of CRC should also include quality assurance and provide for the recording of quality indicators (such as the adenoma and SSL detection rate) for this purpose. In addition, the introduction of screening can also be used to assess suitable methods of approaching the target population and recording family histories as well as the evaluation of the proportion of false-negative iFOBT findings.

In the proposed study design, the control group would consist of the population of another country, which would be associated with certain differences between the compared cohorts in demographic characteristics or health care structures, for example. Even if this reduces the informative value, such a (concurrent) comparison with a situation without risk group screening is necessary in order to gain insights into the benefits (and harms) of CRC screening

in people under the age of 50 with a familial risk of CRC. Bearing in mind all the limitations associated with the proposed study design, the approach outlined could still represent the assessment concept with the highest informative value when comparing all realistic options. The introduction of CRC screening in people under the age of 50 with a familial risk of CRC should in any case be used as an opportunity to generate evidence on the potential benefits and harms of CRC screening in this group of people.

7 Conclusion

Direct evidence on CRC screening in people under 50 with a familial risk of CRC

There is no direct evidence on the systematic screening of people under the age of 50 with a familial risk of CRC (there are no comparative intervention studies of the screening process).

Indirect evidence on CRC screening (transferability)

An extensive search for studies on the transferability of CRC screening findings from people aged 50 and over without a (known) familial risk of CRC to people under 50 with a familial risk overall revealed little evidence on individual aspects of transferability.

Only one aspect of transferability — namely, the diagnostic accuracy and direct adverse effects of established screening tests — is supported by the identified evidence on transferability. For the other transferability aspects, the identified evidence neither supports nor refutes transferability, or there is no evidence. Therefore, in the overall assessment of the rather sparse evidence on key transferability aspects, it remains unclear whether the proven benefits of CRC screening for people aged 50 years or older without a (known) familial risk of CRC could be achieved in a similar way in people under 50 years of age with a familial risk.

Recommendations for an accompanying assessment in the event of an extension of CRC screening

If despite the limited evidence, CRC screening is introduced in Germany for people under 50 with a familial risk of CRC, an accompanying assessment should be carried out. For example, a comparison could be made with another country where no such risk group screening has been established. This report contains detailed recommendations for designing such an assessment.

References for English extract

Please see final report for full reference list.

1. Sung H, Ferlay J, Siegel RL et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Occurrence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021; 71(3): 209-249. https://doi.org/10.3322/caac.21660.

2. Robert Koch Institut. Krebs in Deutschland für 2019/2020 [online]. 2023 [Accessed: 29.01.2024]. URL: https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/krebs_in_deutschland_2023.pdf?__blob=publicationFile.

3. Lin JS, Perdue LA, Henrikson NB et al. Screening for Colorectal Cancer; An Evidence Update for the U.S. Preventive Services Task Force; Report No.: 20-05271-EF-1. Rockville (MD): Agency for Healthcare Research and Quality; 2021.

4. Crockett SD, Nagtegaal ID. Terminology, Molecular Features, Epidemiology, and Management of Serrated Colorectal Neoplasia. Gastroenterology 2019; 157(4): 949-966 e944. https://doi.org/10.1053/j.gastro.2019.06.041.

5. Vogelstein B, Fearon ER, Hamilton SR et al. Genetic alterations during colorectal-tumor development. N Engl J Med 1988; 319(9): 525-532. https://doi.org/10.1056/NEJM198809013190901.

6. Gemeinsamer Bundesausschuss. Richtlinie des Gemeinsamen Bundesausschusses für organisierte Krebsfrüherkennungsprogramme; (oKFE-Richtlinie/oKFE-RL); in der Fassung vom 19. Juli 2018; zuletzt geändert am 12. Mai 2023 [online]. 2023. URL: https://www.g-ba.de/downloads/62-492-3189/oKFE-RL-2023-05-12-iK-2023-07-07.pdf.

7. Leitlinienprogramm Onkologie. S3 Leitlinie Kolorektales Karzinom; Langversion 2.1.; AWMF-Registernummer: 021/007OL [online]. 2019 [Accessed: 30.01.2024]. URL: https://register.awmf.org/assets/guidelines/021-007OLl_S3_Kolorektales-Karzinom-KRK_2019-01-abgelaufen.pdf.

8. Bahadoer RR, Dijkstra EA, van Etten B et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol 2021; 22(1): 29-42. https://doi.org/10.1016/S1470-2045(20)30555-6.

9. Messmann H. Kolorektales Karzinom. In: Messmann H (Ed). Klinische Gastroenterologie. 2021. p. 509-555.

10. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Bewertung des Nutzens einer Früherkennungsuntersuchung für Personen unter 55 Jahren mit familiärem Darmkrebsrisiko; Abschlussbericht [online]. 2013 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/s11-01_abschlussbericht_frueherkennungsuntersuchung-bei-familiaerem-darm.pdf.

11. Roos VH, Mangas-Sanjuan C, Rodriguez-Girondo M et al. Effects of Family History on Relative and Absolute Risks for Colorectal Cancer: A Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol 2019; 17(13): 2657-2667 e2659. https://doi.org/10.1016/j.cgh.2019.09.007.

12. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Darmkrebsfrüherkennung bei Personen unter 55 Jahren mit familiärem Risiko; Aktualisierung; Rapid Report [online]. 2018 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/s17-01_frueherkennung-bei-familiaerem-darmkrebsrisiko-aktualisierung_rapid-report_v1-0.pdf.

13. Schoen RE, Razzak A, Yu KJ et al. Occurrence and Mortality of Colorectal Cancer in People With a Family History of Colorectal Cancer. Gastroenterology 2015; 149(6): 1438-1445.e1. https://doi.org/10.1053/j.gastro.2015.07.055.

14. Henrikson NB, Webber EM, Goddard KA et al. Family history and the natural course of colorectal cancer; systematic review. Genet Med 2015; 17(9): 702-712. https://doi.org/10.1038/gim.2014.188.

15. Cha JM, Lee JI, Joo KR et al. First-degree relatives of colorectal cancer patients are likely to show advanced colorectal neoplasia despite a negative fecal immunochemical test. Digestion 2012; 86(4): 283-287. https://doi.org/10.1159/000341738.

16. Cubiella J, Castro I, Hernandez V et al. Diagnostic accuracy of fecal immunochemical test in average- and familial-risk colorectal cancer screening. United European Gastroenterology Journal 2014; 2(6): 522-529. https://doi.org/10.1177/2050640614553285.

17. Hilsden RJ, Dube C, Heitman SJ et al. The association of colonoscopy quality indicators with the detection of screen-relevant lesions, adverse events, and postcolonoscopy cancers in an asymptomatic Canadian colorectal cancer screening population. Gastrointestinal Endoscopy 2015; 82(5): 887-894. https://doi.org/10.1016/j.gie.2015.03.1914.

18. Jung YS, Lee J, Lee HA et al. Interval Cancer Rate and Diagnostic Performance of Fecal Immunochemical Test According to Family History of Colorectal Cancer. Journal of Clinical Medicine 2020; 9(10). https://doi.org/10.3390/jcm9103302.

19. Ng SC, Ching JY, Chan V et al. Diagnostic accuracy of faecal immunochemical test for screening people with a family history of colorectal cancer. Aliment Pharmacol Ther 2013; 38(7): 835-841. https://doi.org/10.1111/apt.12446.

20. Hoffmeister M, Schmitz S, Karmrodt E et al. Male sex and smoking have a larger impact on the prevalence of colorectal neoplasia than family history of colorectal cancer. Clin Gastroenterol Hepatol 2010; 8(10): 870-876. https://doi.org/10.1016/j.cgh.2010.07.004.

21. Wark PA, Wu K, van 't Veer P et al. Family history of colorectal cancer: a determinant of advanced adenoma stage or adenoma multiplicity? Int J Cancer 2009; 125(2): 413-420. https://doi.org/10.1002/ijc.24288.

22. Hemminki K, Santi I, Weires M et al. Tumor location and patient characteristics of colon and rectal adenocarcinomas in relation to survival and TNM classes. BMC Cancer 2010; 10: 688. https://doi.org/10.1186/1471-2407-10-688.

23. Clinical and pathological analyses of patients with a family history of colorectal cancer. Registry Committee, Japanese Research Society for Cancer of the Colon and Rectum. Jpn J Clin Oncol 1993; 23(6): 342-349.

24. Bass AJ, Meyerhardt JA, Chan JA et al. Family history and survival after colorectal cancer diagnosis. Cancer 2008; 112(6): 1222-1229. https://doi.org/10.1002/cncr.23294.

25. Kao PS, Lin JK, Wang HS et al. The impact of family history on the outcome of patients with colorectal cancer in a veterans' hospital. Int J Colorectal Dis 2009; 24(11): 1249-1254. https://doi.org/10.1007/s00384-009-0774-3.

26. Zell JA, Honda J, Ziogas A et al. Survival after colorectal cancer diagnosis is associated with colorectal cancer family history. Cancer Epidemiol Biomarkers Prev 2008; 17(11): 3134-3140. https://doi.org/10.1158/1055-9965.EPI-08-0587.

27. Cubiella J, Castro I, Hernandez V et al. Diagnostic accuracy of fecal immunochemical test in average- and familial-risk colorectal cancer screening. United European Gastroenterology Journal 2014; 2(6): 522-529. https://doi.org/10.1177/2050640614553285.

28. Jung YS, Lee J, Lee HA et al. Interval Cancer Rate and Diagnostic Performance of Fecal Immunochemical Test According to Family History of Colorectal Cancer. J Clin Med 2020; 9(10). https://doi.org/10.3390/jcm9103302.

29. Wong MC, Tsoi KK, Ng SS et al. A comparison of the acceptance of immunochemical faecal occult blood test and colonoscopy in colorectal cancer screening: a prospective study among Chinese. Aliment Pharmacol Ther 2010; 32(1): 74-82. https://doi.org/10.1111/j.1365-2036.2010.04312.x.

30. Ramsey SD, Burke W, Pinsky L et al. Family history assessment to detect increased risk for colorectal cancer: Conceptual considerations and a preliminary economic analysis. Cancer Epidemiology Biomarkers & Prevention 2005; 14(11): 2494-2500. https://doi.org/10.1158/1055-9965.Epi-05-0418.

31. Baronas VA, Arif AA, Bhang E et al. Symptom Burden and Time from Symptom Onset to Cancer Diagnosis in Patients with Early-Onset Colorectal Cancer: A Multicenter Retrospective Analysis. Curr Oncol 2024; 31(4): 2133-2144. https://doi.org/10.3390/curroncol31040158.

32. Mauri G, Sartore-Bianchi A, Russo AG et al. Early-onset colorectal cancer in young people. Mol Oncol 2019; 13(2): 109-131. https://doi.org/10.1002/1878-0261.12417.

33. Li PW, Li SY, Chen JM et al. Association between family history and prognosis of patients with colorectal cancer: a systematic review and meta-analysis. Translational Cancer Research 2022; 11(1). https://doi.org/10.21037/tcr-21-1546.

34. Crispin A, Rehms R, Hoffmann S et al. Vorsorge bei familiärem Risiko für das kolorektale Karzinom; Evaluation des Programms FARKOR zur Sekundärprävention kolorektaler Karzinome bei 25- bis 50-Jährigen. Dtsch Arztebl 2023; 120(46): 786-792.

35. Rehms R, Hoffmann S, Lindörfer D et al. Vorsorge bei familiärem Risiko für das kolorektale Karzinom (KRK); Evaluationsbericht Teil 1: Epidemiologische Evaluation [online]. 2023 [Accessed: 18.07.24]. URL: https://innovationsfonds.g-ba.de/downloads/beschluss-dokumente/380/2023-02-23_FARKOR_Evaluationsbericht.pdf.

36. Sroczynski G, Hallsson LR, Mühlberger N et al. Vorsorge bei familiärem Risiko für das kolorektale Karzinom (KRK); Evaluationsbericht Teil 2: Gesundheitsökonomische Evaluation [online]. 2023 [Accessed: 18.08.2024]. URL: https://innovationsfonds.g-ba.de/downloads/beschluss-dokumente/380/2023-02-23_FARKOR_Evaluationsbericht.pdf.

37. Gemeinsamer Bundesausschuss. Beschluss des Innovationsausschusses beim Gemeinsamen Bundesausschuss gemäß § 92b Absatz 3 SGB V zum abgeschlossenen Projekt FARKOR (01NVF17026) [online]. 2023 [Accessed: 18.07.2024]. URL: https://innovationsfonds.g-ba.de/downloads/beschluss-dokumente/378/2023-02-23_FARKOR.pdf.

38. Sroczynski G, Hallsson LR, Mühlberger N et al. Long-term benefits and harms of early colorectal cancer screening in German people with a familial cancer risk. Int J Cancer 2024; 154(3): 516-529. https://doi.org/10.1002/ijc.34747.

39. Briggs AH, Weinstein MC, Fenwick EA et al. Model parameter estimation and uncertainty; a report of the ISPOR-SMDM Modelling Good Research Practices Task Force-6. Value Health 2012; 15(6): 835-842. https://doi.org/10.1016/j.jval.2012.04.014.

40. Brozek JL, Canelo-Aybar C, Akl EA et al. GRADE Guidelines 30; the GRADE approach to assessing the certainty of modeled evidence-An overview in the context of health decision-making. J Clin Epidemiol 2021; 129: 138-150. https://doi.org/10.1016/j.jclinepi.2020.09.018.

41. Dillon M, Flander L, Buchanan DD et al. Family history-based colorectal cancer screening in Australia: A modelling study of the costs, benefits, and harms of different participation scenarios. PLoS Med 2018; 15(8). https://doi.org/10.1371/journal.pmed.1002630.

42. Naber SK, Kuntz KM, Henrikson NB et al. Cost Effectiveness of Age-Specific Screening Intervals for People With Family Histories of Colorectal Cancer. Gastroenterology 2018; 154(1). https://doi.org/10.1053/j.gastro.2017.09.021.

43. Ouakrim DA, Boussioutas A, Lockett T et al. Cost-effectiveness of family history-based colorectal cancer screening in Australia. BMC Cancer 2014; 14. https://doi.org/10.1186/1471-2407-14-261.

44. Ramsey SD, Wilschut J, Boer R et al. A Decision-Analytic Evaluation of the Cost-Effectiveness of Family History-Based Colorectal Cancer Screening Programs. Am J Gastroenterol 2010; 105(8): 1861-1869. https://doi.org/10.1038/ajg.2010.185.

45. Wilschut JA, Steyerberg EW, van Leerdam ME et al. How Much Colonoscopy Screening Should Be Recommended to People With Various Degrees of Family History of Colorectal Cancer? Cancer 2011; 117(18): 4166-4174. https://doi.org/10.1002/cncr.26009.

46. Knudsen AB, Rutter CM, Peterse EFP et al. Colorectal Cancer Screening; An Updated Modelling Study for the US Preventive Services Task Force. JAMA 2021; 325(19): 1998-2011. https://doi.org/10.1001/jama.2021.5746.

47. Knudsen AB, Rutter CM, Peterse EFP et al. Colorectal Cancer Screening; An Updated Decision Analysis for the U.S. Preventive Services Task Force; Technical Report. Rockville (MD): Agency for Healthcare Research and Quality (US); 2021.

48. National Institute for Medical Research Development. Implementation of a population-level colonoscopic screening in first-degree relatives of colorectal cancer patients in Golestan province of Iran: Feasibility and Effectiveness [online]. 2019 [Accessed: 05.06.2024]. URL: https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT20120225009124N3.

49. Bretthauer M, Loberg M, Wieszczy P et al. Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death. N Engl J Med 2022; 387(17): 1547-1556. https://doi.org/10.1056/NEJMoa2208375.

50. Palsson B. [Screening for colorectal cancer nationally instituted in Sweden]. Lakartidningen 2023; 120.

51. Statistics Sweden. Multi-generation register 2016; A description of content and quality; Population and Welfare, Background Facts 2017:2 [online]. 2017 [Accessed: 22.10.2024]. URL: https://www.scb.se/contentassets/95935956ea2b4fa9bcaab51afa259981/ov9999_2016a01_br_be96br1702eng.pdf.

52. The National Board of Health and Welfare. Statistical registers production and quality National Cancer Register [online]. 2023 [Accessed: 22.10.2024]. URL: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/dokument-webb/ovrigt/production-and-quality-can.pdf.

53. Tian Y, Kharazmi E, Sundquist K et al. Familial colorectal cancer risk in half siblings and siblings: nationwide cohort study. BMJ 2019; 364: l803. https://doi.org/10.1136/bmj.l803.

54. Tian Y, Kharazmi E, Brenner H et al. Importance of Family History of Colorectal Carcinoma In Situ Versus Invasive Colorectal Cancer: A Nationwide Cohort Study. J Natl Compr Canc Netw 2021; 19(11): 1252-1257. https://doi.org/10.6004/jnccn.2021.7004.

55. Tian Y, Kharazmi E, Brenner H et al. Calculating the Starting Age for Screening in Relatives of Patients With Colorectal Cancer Based on Data From Large Nationwide Data Sets. Gastroenterology 2020; 159(1): 159-168 e153. https://doi.org/10.1053/j.gastro.2020.03.063.

56. Wong SS, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc 2006; 94(4): 451-455.

57. Lefebvre C, Glanville J, Briscoe S et al. Cochrane Handbook for Systematic Reviews of Interventions; Version 6.4; Technical Supplement to Chapter 4: Searching for and selecting studies [online]. 2024 [Accessed: 17.04.2024]. URL: https://training.cochrane.org/chapter04-tech-supplonlinepdfv64-final-200224.

58. Haynes RB, Wilczynski NL. Optimal search strategies for retrieving scientifically strong studies of diagnosis from Medline: analytical survey. BMJ 2004; 328(7447): 1040. https://doi.org/10.1136/bmj.38068.557998.EE.

The full report (German version) is published under
https://www.iqwig.de/en/projects/s23-01.html

Appendix A Search strategies

A.1 Searches in bibliographic databases

Project preparation search for systematic reviews

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to December 01, 2023

The following filter was adopted:

- Systematic review: Wong [56] – High specificity strategy

#	Searches
1	exp Colorectal Neoplasms/
2	((colorectal* or rectal* or colon* or sigma* or sigmo* or rectum*) adj5 (cancer? or metastas* or carcinom* or neoplas* or malignan* or tumour? or tumour? or adenomatous* or adenocarcinoma* or adenoma* or polyp*)).ab,ti.
3	or/1-2
4	(famil* adj3 histor*).ab,ti.
5	((famil* or sibling* or parent*) adj5 (risk* or aggregation or cancer)).ab,ti.
6	(degree adj3 relative*).ab,ti.
7	or/4-6
8	Surveys and Questionnaires/
9	(questionnaire* or surveillance or survey).ab,ti.
10	exp Colonoscopy/
11	(colonoscop* or sigmoidoscop* or endoscop*).ab,ti.
12	Colonography, Computed Tomographic/
13	(colography or colonography).ab,ti.
14	DNA Mutational Analysis/
15	exp DNA/an
16	chromoscopy.ab,ti.
17	Occult Blood/
18	Guaiac/
19	Reagent Kits, Diagnostic/
20	(stool or fece* or faece* or fecal* or faecal* or blood or occult or bleed* or fob* or guaiac*).ab,ti.
21	immunochemical*.ab,ti.
22	(haemoccult* or hemoccult*).ab,ti.
23	or/8-22
24	and/3,7,23
25	cochrane database of systematic reviews.jn.
26	(search or MEDLINE or systematic review).tw.

#	Searches
27	meta analysis.pt.
28	or/25-27
29	28 not (exp animals/ not humans.sh.)
30	and/24,29
31	30 and (english or german or multilingual or undetermined).lg.
32	..l/ 31 yr=2018-Current

2. International HTA Database

Search interface: INAHTA

#	Searches
1	Colorectal Neoplasms[mhe]
2	((colorectal* or rectal* or colon* or sigma* or sigmo* or rectum*) AND (cancer* or metastas* or carcinom* or neoplas* or malignan* or tumour* or tumour* or adenomatous* or adenocarcinoma* or adenoma* or polyp*))
3	#2 OR #1
4	famil* AND histor*
5	(famil* or sibling* or parent*) AND (risk* or aggregation or cancer)
6	degree AND relative*
7	#6 OR #5 OR #4
8	#7 AND #3
9	(*) FROM 2018 TO 2023
10	#9 AND #8

Schritt A: Comprehensive information retrieval – Search for primary studies for sub-objective 1 and sub-objective

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL, 1946 to February 27, 2024

The following filter was adopted:

- RCT: Lefebvre [57] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2023 revision)

#	Searches
1	exp Colorectal Neoplasms/
2	((colorectal* or rectal* or colon* or sigma* or sigmo* or rectum*) adj5 (cancer? or metastas* or carcinom* or neoplas* or malignan* or tumour? or tumour? or adenomatous* or adenocarcinoma* or adenoma* or polyp*)).ab,ti.
3	or/1-2
4	(famil* adj3 histor*).ab,ti.
5	((famil* or sibling* or parent*) adj5 (risk* or aggregation or cancer)).ab,ti.
6	(degree adj3 relative*).ab,ti.
7	or/4-6
8	exp Colonoscopy/
9	(colonoscop* or sigmoidoscop* or endoscop*).ab,ti.
10	Colonography, Computed Tomographic/
11	(colography or colonography).ab,ti.
12	DNA Mutational Analysis/
13	exp DNA/an
14	chromoscopy.ab,ti.
15	Occult Blood/
16	Guaiac/
17	Reagent Kits, Diagnostic/
18	(stool or fece* or faece* or fecal* or faecal* or blood or occult or bleed* or fob* or guaiac*).ab,ti.
19	immunochemical*.ab,ti.
20	(haemoccult* or hemoccult*).ab,ti.
21	or/8-20
22	exp Randomized controlled Trial/
23	Controlled Clinical Trial.pt.
24	(randomized or placebo or randomly or trial or groups).ab.
25	drug therapy.fs.
26	or/22-25
27	exp animals/ not humans/
28	26 not 27
29	and/3,7,21,28
30	exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp assessment studies as topic/ or exp statistics as topic/
31	((control and (group* or study)) or (time and factors) or programme or survey* or ci or cohort or comparative stud* or assessment studies or follow-up*).mp.
32	or/30-31
33	and/3,7,21,32
34	or/29,33
35	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/

#	Searches
36	hi.fs. or case report.mp.
37	or/35-36
38	34 not 37
39	38 and (english or german or multilingual or undetermined).lg.
40	39 and 20171115:3000.(dt).

2. Embase

Search interface: Ovid

- Embase 1974 to 2024 February 27

The following filter was adopted:

- RCT: Wong [56] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	exp Colon Cancer/
2	exp Rectum Cancer/
3	exp Colorectal Adenoma/
4	exp Colon Polyp/
5	((colorectal* or rectal* or colon* or sigma* or sigmo* or rectum*) adj5 (cancer? or metastas* or carcinom* or neoplas* or malignan* or tumour? or tumour? or adenomatous* or adenocarcinoma* or adenoma* or polyp*)).ab,ti.
6	or/1-5
7	Family history/
8	Hereditary Tumour Syndrome/
9	Familial disease/
10	(famil* adj3 histor*).ab,ti.
11	((famil* or sibling* or parent*) adj5 (risk* or aggregation or cancer)).ab,ti.
12	(degree adj3 relative*).ab,ti.
13	or/7-12
14	exp Colonoscopy/
15	Sigmoidoscopy/
16	(colonoscop* or sigmoidoscop* or endoscop*).ab,ti.
17	computed tomographic colonography/
18	(colography or colonography).ab,ti.
19	DNA determination/
20	DNA/
21	chromoscopy.ab,ti.
22	Occult blood/

#	Searches
23	Occult blood test/
24	(stool or fece* or faece* or fecal* or faecal* or blood or occult or bleed* or fob* or guaiac*).ab,ti.
25	(haemoccult* or hemoccult*).ab,ti.
26	immunochemical*.ab,ti.
27	or/14-26
28	(random* or double-blind*).tw.
29	placebo*.mp.
30	or/28-29
31	and/6,13,27,30
32	31 not medline.cr.
33	32 not (exp animal/ not exp human/)
34	33 not (Conference Abstract or Conference Review or Editorial).pt.
35	34 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg.
36	35 and 20171115:3000.(dc).

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Registry of Controlled Trials: Issue 2 of 12, February 2024

#	Searches
#1	[mh "Colorectal Neoplasms"]
#2	((colorectal* or rectal* or colon* or sigma* or sigmo* or rectum*) NEAR/5 (cancer? or metastas* or carcinom* or neoplas* or malignan* or tumour* or tumour* or adenomatous* or adenocarcinoma* or adenoma* or polyp*)):ti,ab
#3	#1 or #2
#4	(famil* NEAR/3 histor*):ti,ab
#5	((famil* or sibling* or parent*) NEAR/5 (risk* or aggregation or cancer)):ti,ab
#6	(degree NEAR/3 relative*):ti,ab
#7	#4 or #5 or #6
#8	[mh "Colonoscopy"]
#9	(colonoscop* or sigmoidoscop* or endoscop*):ti,ab
#10	[mh ^"Colonography, Computed Tomographic"]
#11	(colography or colonography):ti,ab
#12	[mh ^"DNA Mutational Analysis"]

#	Searches
#13	[mh DNA]
#14	chromoscopy:ti,ab
#15	[mh ^"Occult Blood"]
#16	[mh ^"Guaiac"]
#17	[mh ^"Reagent Kits, Diagnostic"]
#18	(stool or fece* or faece* or fecal* or faecal* or blood or occult or bleed* or fob* or guaiac*):ti,ab
#19	immunochemical*:ti,ab
#20	(haemoccult* or hemoccult*):ti,ab
#21	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#22	#3 and #7 and #21
#23	#22 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
#24	#23 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown)))
#25	#24 with Publication Year from 2017 to 2024, in Trials

Step B: Focused information retrieval– Search for systematic reviews for sub-objective 2b to sub-objective 2d

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to March 06, 2024

The following filter was adopted:

- Systematic review: Wong [56] – High specificity strategy

#	Searches
1	exp Colorectal Neoplasms/
2	((colorectal* or rectal* or colon* or sigma* or sigmo* or rectum*) adj5 (cancer? or metastas* or carcinom* or neoplas* or malignan* or tumour? or tumour? or adenomatous* or adenocarcinoma* or adenoma* or polyp*)).ab,ti.
3	or/1-2
4	(famil* adj3 histor*).ab,ti.
5	((famil* or sibling* or parent*) adj5 (risk* or aggregation or cancer)).ab,ti.
6	(degree adj3 relative*).ab,ti.
7	or/4-6
8	cochrane database of systematic reviews.jn.
9	(search or MEDLINE or systematic review).tw.

#	Searches
10	meta analysis.pt.
11	or/8-10
12	11 not (exp animals/ not humans.sh.)
13	and/3,7,12
14	13 and (english or german or multilingual or undetermined).lg.

2. International HTA Database

Search interface: INAHTA

#	Searches
1	Colorectal Neoplasms[mhe]
2	(colorectal* or rectal* or colon* or sigma* or sigmo* or rectum*) and (cancer* or metastas* or carcinom* or neoplas* or malignan* or tumour* or tumour* or adenomatous* or adenocarcinoma* or adenoma* or polyp*)
3	#2 OR #1
4	famil* and histor*
5	(famil* or sibling* or parent*) and (risk* or aggregation or cancer)
6	degree and relative*
7	#6 OR #5 OR #4
8	#7 AND #3

Step C: Focused information retrieval – Search for primary studies for sub-objective 2c

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to March 19, 2024

The following filter was adopted:

- Diagnostic studies: Haynes [58] – Search strategie yielding highest sensitivity with combinations of terms.

#	Searches
1	exp Colorectal Neoplasms/
2	((colorectal* or rectal* or colon* or sigma* or sigmo* or rectum*) adj5 (cancer? or metastas* or carcinom* or neoplas* or malignan* or tumour? or tumour? or adenomatous* or adenocarcinoma* or adenoma* or polyp*)).ab,ti.
3	or/1-2
4	(famil* adj3 histor*).ab,ti.
5	((famil* or sibling* or parent*) adj5 (risk* or aggregation or cancer)).ab,ti.

#	Searches
6	(degree adj3 relative*).ab,ti.
7	or/4-6
8	exp Colonoscopy/
9	(colonoscop* or sigmoidoscop* or endoscop*).ab,ti.
10	Colonography, Computed Tomographic/
11	(colography or colonography).ab,ti.
12	DNA Mutational Analysis/
13	exp DNA/an
14	chromoscopy.ab,ti.
15	Occult Blood/
16	Guaiac/
17	Reagent Kits, Diagnostic/
18	(stool or fece* or faece* or fecal* or faecal* or blood or occult or bleed* or fob* or guaiac*).ab,ti.
19	immunochemical*.ab,ti.
20	(haemoccult* or hemoccult*).ab,ti.
21	or/8-20
22	Mass Screening/
23	Early Detection of Cancer/
24	screen*.mp.
25	or/22-24
26	(sensitiv: or diagnos:).mp. or di.fs.
27	and/3,7,21,25-26
28	27 not (exp animals/ not humans.sh.)
29	28 and (english or german or multilingual or undetermined).lg.
30	29 and 2009:3000.(dt).

2. The Cochrane Library

Search interface: Wiley

- Cochrane Central Registry of Controlled Trials: Issue 2 of 12, February 2024

The following filter was adopted:

- Diagnostic studies: Haynes [58] – Search strategy yielding highest sensitivity with combinations of terms [adapted].

#	Searches
#1	[mh "Colorectal Neoplasms"]
#2	((colorectal* or rectal* or colon* or sigma* or sigmo* or rectum*) NEAR/5 (cancer? or metastas* or carcinom* or neoplas* or malignan* or tumour? or tumour? or adenomatous* or adenocarcinoma* or adenoma* or polyp*)):ti,ab
#3	#1 or #2
#4	(famil* NEAR/3 histor*):ti,ab
#5	((famil* or sibling* or parent*) NEAR/5 (risk* or aggregation or cancer)):ti,ab
#6	(degree NEAR/3 relative*):ti,ab
#7	#4 or #5 or #6
#8	[mh "Colonoscopy"]
#9	(colonoscop* or sigmoidoscop* or endoscop*):ti,ab
#10	[mh ^"Colonography, Computed Tomographic"]
#11	(colography or colonography):ti,ab
#12	[mh ^"DNA Mutational Analysis"]
#13	[mh DNA]
#14	chromoscopy:ti,ab
#15	[mh ^"Occult Blood"]
#16	[mh ^"Guaiac"]
#17	[mh ^"Reagent Kits, Diagnostic"]
#18	(stool or fece* or faece* or fecal* or faecal* or blood or occult or bleed* or fob* or guaiac*):ti,ab
#19	immunochemical*:ti,ab
#20	(haemoccult* or hemoccult*):ti,ab
#21	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#22	[mh ^"Mass Screening"]
#23	[mh ^"Early Detection of Cancer"]
#24	screen*:ti,ab
#25	#22 or #23 or #24
#26	(sensitiv* or diagnos*):ti,ab
#27	MeSH descriptor: [] explode all trees and with qualifier(s): [diagnosis - DI]
#28	#26 or #27
#29	#3 and #7 and #21 and #25 and #28
#30	#29 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
#31	#30 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown)))
#32	#31 with Publication Year from 2009 to 2024, in Trials

Step C: Focused information retrieval – Search for primary studies for sub-objective 2d

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to March 22, 2024

The following filter was adopted:

- RCT: Lefebvre [57] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2023 revision)

#	Searches
1	exp Colorectal Neoplasms/
2	((colorectal* or rectal* or colon* or sigma* or sigmo* or rectum*) adj5 (cancer? or metastas* or carcinom* or neoplas* or malignan* or tumour? or tumour? or adenomatous* or adenocarcinoma* or adenoma* or polyp*)).ab,ti.
3	or/1-2
4	(famil* adj3 histor*).ab,ti.
5	((famil* or sibling* or parent*) adj5 (risk* or aggregation or cancer)).ab,ti.
6	(degree adj3 relative*).ab,ti.
7	or/4-6
8	exp Randomized Controlled Trial/
9	Controlled Clinical Trial.pt.
10	(randomized or placebo or randomly).ab.
11	Clinical Trials as Topic/
12	trial.ti.
13	or/8-12
14	exp Animals/ not Humans/
15	13 not 14
16	and/3,7,15
17	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
18	hi.fs. or case report.mp.
19	or/17-18
20	16 not 19
21	20 and (english or german or multilingual or undetermined).lg.
22	21 and 2010:3000.(dp).

2. The Cochrane Library

Search interface: Wiley

- Cochrane Central Registry of Controlled Trials: Issue 2 of 12, February 2024

#	Searches
#1	[mh "Colorectal Neoplasms"]
#2	((colorectal* or rectal* or colon* or sigma* or sigmo* or rectum*) NEAR/5 (cancer? or metastas* or carcinom* or neoplas* or malignan* or tumour? or tumour? or adenomatous* or adenocarcinoma* or adenoma* or polyp*)):ti,ab
#3	#1 or #2
#4	(famil* NEAR/3 histor*):ti,ab
#5	((famil* or sibling* or parent*) NEAR/5 (risk* or aggregation or cancer)):ti,ab
#6	(degree NEAR/3 relative*):ti,ab
#7	#4 or #5 or #6
#8	#3 and #7
#9	#8 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
#10	#9 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown)))
#11	#10 with Publication Year from 2010 to 2024, in Trials

A.2 Searches in study registries

Step A: Comprehensive information retrieval – search for primary studies for sub-objective 1 and sub-objective 2a

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Basic Search

Search strategy
(family OR familiar OR familial OR sibling OR first degree) [Other terms] AND (CRC OR rectal cancer OR colon cancer OR sigmoid colon OR rectosigmoid OR rectum cancer) [Condition/disease] AND (colonoscopy OR sigmoidoscopy OR endoscopy OR colography OR colonography OR chromoscopy OR stool OR blood OR occult OR bleed OR fob OR guaiac OR immunochemical OR haemoccult OR hemoccult) [Intervention/treatment]

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: https://trialsearch.who.int
- Type of search: Standard Search

Search strategy
(colorectal OR rectal OR colon OR sigmoid colon OR rectosigmoid OR rectum) AND (famil* OR sibling OR first degree)

Step C: Focused information retrieval – search for primary studies for sub-objective 2c and sub-objective 2d

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Basic Search

Search strategy
CRC OR rectal cancer OR colon cancer OR sigmoid colon OR rectosigmoid OR rectum cancer [Condition/disease] AND family OR sibling OR first degree [Other terms] / Study Results: With results

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: https://trialsearch.who.int
- Type of search: Standard Search

Search strategy
(colorectal OR rectal OR colon OR sigmoid colon OR rectosigmoid OR rectum) AND (famil* OR sibling OR first degree) / With results only