Norwegian Medical Products Agency

Protocol for Health Technology Assessment

PIK3CA, PIK3R1, and PTEN Gene Alteration Testing in Patients Undergoing Colorectal Cancer Surgery to Evaluate Adjuvant Acetylsalicylic Acid Treatment

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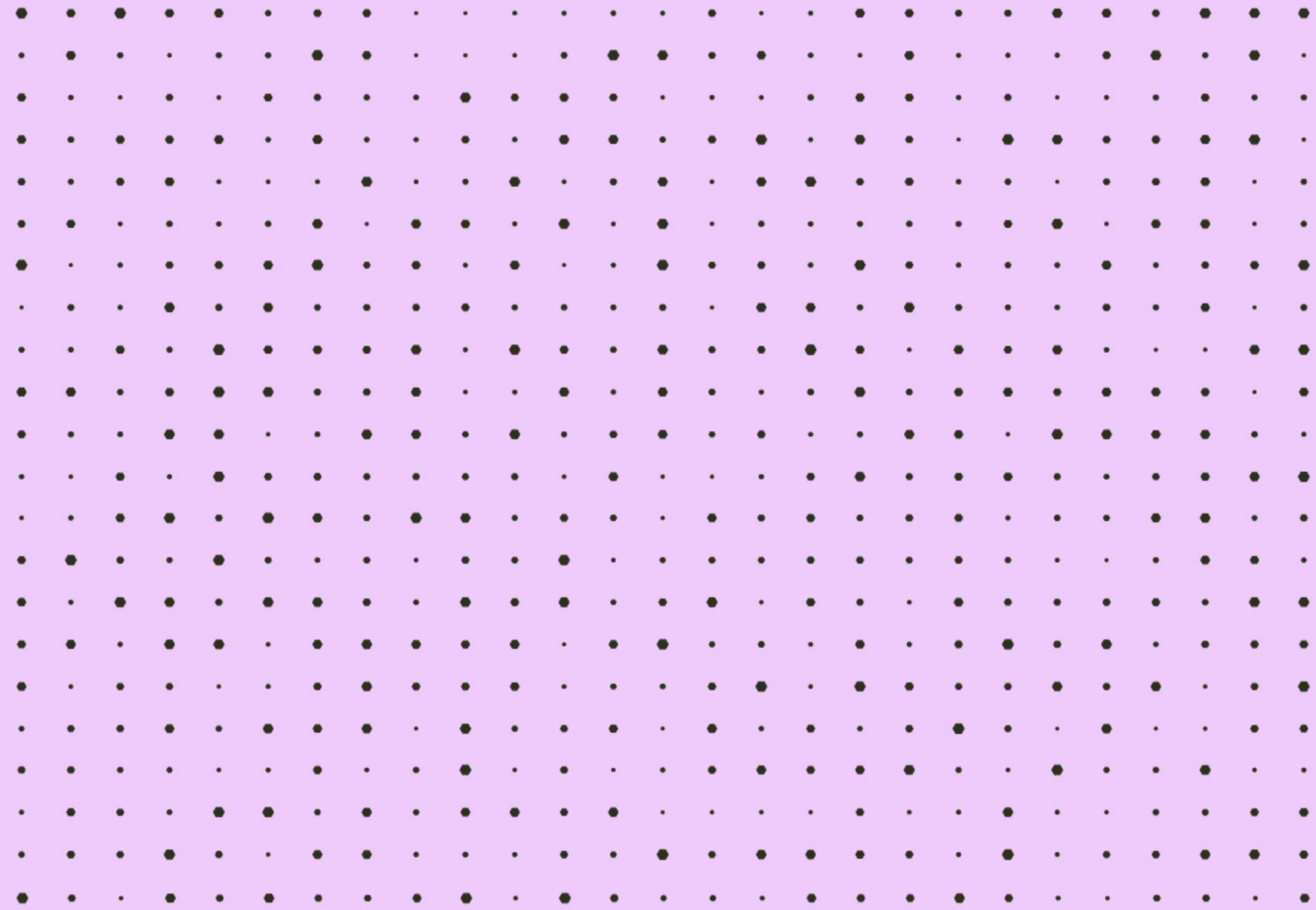

Innholdsfortegnelse

Summary

Norway has one of the highest incidences of colorectal cancer (CRC) in the world. Although surgery is intended to be a curative treatment for CRC, around one-fifth of patients experience disease recurrence. Acetylsalicylic acid (ASA) has shown promise as an adjuvant treatment for patients with *PIK3CA*, *PIK3R1*, and *PTEN* alterations. However, the health economic sustainability of incorporating genetic testing and adjuvant ASA treatment into clinical practice remains unclear, highlighting the need for an evidence-based evaluation of the health economic aspects alongside an assessment of clinical effectiveness and safety.

In this protocol, we outline the methodological approaches to be used in the health technology assessment (HTA). The HTA will address the prioritisation criteria of health benefit, severity, and resource use. An expert group, consisting of clinical specialists and patient representatives, will provide input to the HTA report.

We will conduct a systematic review to assess the clinical effectiveness and safety of adjuvant ASA treatment compared to placebo in post-surgical CRC patients with *PIK3CA*, *PIK3R1*, and *PTEN* gene alterations. Systematic literature searches will be conducted, and results from studies meeting the inclusion criteria will be compiled after an assessment of systematic biases at the outcome level. Finally, we will evaluate the level of confidence in the results.

We will assess the health economic consequences of testing *PIK3CA*, *PIK3R1*, and *PTEN* alterations as a basis for determining adjuvant ASA treatment in post-surgical CRC patients, compared to current clinical practice. We will conduct a model-based cost-effectiveness analysis. The model will estimate costs and quality-adjusted life years over a lifetime horizon from an extended healthcare sector perspective, using Norwegian unit prices and following national treatment guidelines. The analysis will incorporate data from systematic reviews, registry data, and expert input.

We will also address organisational aspects of implementing *PIK3CA*, *PIK3R1*, and *PTEN* alteration testing, along with subsequent ASA treatment for post-surgical CRC patients with these alterations. This assessment will be based on input from the expert group, relevant guidelines, and current practices in colorectal cancer treatment.

Finally, we aim to summarise the experiences of CRC patients, focusing on their perspectives regarding the disease, current treatment options, and expectations for adjuvant ASA treatment in patients with *PIK3CA*, *PIK3R1*, and *PTEN* alterations.

Title:

PIK3CA, *PIK3R1*, and *PTEN* Gene Alteration Testing in Patients Undergoing Colorectal Cancer Surgery to Evaluate Adjuvant Acetylsalicylic Acid Treatment: Protocol for a Health Technology Assessment

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Commissioner:
The Ordering Forum in the national system for managed introduction of health technologies within the specialist health care service

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Date commissioned:
19.01.2026

Start date:
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Target date:
19.04.2027

Team:
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Approved by:
Carolin Hagen, Acting Head of Unit, NOMA

Sammendrag

Norge har en av de høyeste forekomstene av tykk- og endetarmskreft i verden. Selv om kirurgi er ment å være en kurativ behandling for tykk- og endetarmskreft, opplever rundt en femtedel av pasientene tilbakefall av sykdommen. Acetylsalisylsyre har vist seg lovende som adjuvant behandling for pasienter med *PIK3CA*-, *PIK3R1*- og *PTEN*-endringer. Den helseøkonomiske bærekraften ved å innlemme genetisk testing og adjuvant acetylsalisylsyrebehandling i klinisk praksis er imidlertid uklar, noe som understreker behovet for en evidensbasert evaluering av de helseøkonomiske aspektene sammen med en vurdering av den kliniske effekten og sikkerheten.

I denne protokollen skisserer vi den metodiske fremgangsmåten som skal benyttes i den fullstendige metodevurderingen. Metodevurderingen vil belyse prioriteringskriteriene nytte (helsegevinst), alvorlighet og ressursbruk. En ekspertgruppe, bestående av kliniske eksperter og sluttbrukere, vil bidra med innspill til metodevurderingen.

Vi vil utarbeide en systematisk oversikt for å vurdere den kliniske effekten og sikkerheten av adjuvant acetylsalisylsyrebehandling sammenlignet med placebo hos pasienter operert for tykk- og endetarmskreft med genendringer i PIK3CA, PIK3R1 og PTEN. Systematiske litteratursøk vil bli gjennomført, og resultater fra studier som oppfyller inklusjonskriteriene vil bli sammenstilt etter en vurdering av systematiske skjevheter på utfallsnivå. Til slutt vil vi evaluere graden av tillit til resultatene.

Vi vil gjennomføre en modellbasert kostnadseffektivitetsanalyse for å vurdere helseøkonomiske konsekvenser av testing for *PIK3CA*-, *PIK3R1*- og *PTEN*-alterasjoner som grunnlag for adjuvant acetylsalisylsyrebehandling hos pasienter med tarmskreft etter kirurgi, sammenlignet med dagens kliniske praksis. Modellen vil estimere kostnader og kvalitetsjusterte leveår over et livstidsperspektiv fra et utvidet helseperspektiv, basert på norske enhetspriser og i tråd med nasjonale behandlingsretningslinjer. Analysen vil inkludere data fra systematiske oversikter, registerdata og ekspertinnspill. I tillegg vil en budsjettvirkningsanalyse estimere de økonomiske konsekvensene av å innføre tiltaket over en femårsperiode.

Vi vil også belyse organisatoriske aspekter ved innføring av gentesting i *PIK3CA*, *PIK3R1* og *PTEN* og påfølgende acetylsalisylsyrebehandling for pasienter med endringer i disse genene. Vurderingen vil inkludere innspill fra ekspertgruppen, relevante retningslinjer og nåværende praksis for behandling av tykk- og endetarmskreft.

Vi vil også belyse erfaringene til pasienter med tykk- og endetarmskreft, med fokus på deres perspektiver om sykdommen, nåværende behandlingsalternativer og forventninger til adjuvant acetylsalisylsyrebehandling hos pasienter med endringer i *PIK3CA*, *PIK3R1* og *PTEN*.

Tittel:

Testing av genendringer i *PIK3CA*, *PIK3R1* og *PTEN* hos pasienter operert for tykk- og endetarmskreft for vurdering av adjuvant behandling med acetylsalisylsyre: prosjektplan for fullstendig metodevurdering.

Oppdragsgiver:
Bestillerforum for nye metoder

Bestillingsdato:
19.01.2026

Startdato:
22.04.2026

Leveringsfrist:
19.04.2027

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Godkjent av:
Carolin Hagen, fungerende enhetsleder, DMP

Commission

The Division of Health Economics and Analysis at the Norwegian Medical Products Agency (NOMA) was commissioned by the National System for Managed Introduction of New Methods in the Specialist Health Care Service in Norway (called "*Nye metoder*" in Norwegian) on January 19, 2026, to conduct a health technology assessment (HTA) on *PIK3CA*, *PIK3R1*, and *PTEN* gene alteration testing in patients undergoing colorectal cancer surgery to evaluate adjuvant acetylsalicylic acid (ASA) treatment. The commission is the result of a proposal submitted by the Norwegian Gastrointestinal Cancer Group.

The HTA will include assessments of clinical effectiveness, safety, and health economics, as well as organisational consequences. An associated price note is to be prepared by the Norwegian Hospital Procurement Trust (called "*Sykehusinnkjøp HF*" in Norwegian). The HTA will be used as a tool for informed decision-making by the regional health authorities in "*Nye metoder*."

The Division of Health Economics and Analysis follows an established framework when conducting HTAs, described in the Norwegian Institute of Public Health's methods manual (called "*Slik oppsummerer vi forskning"* (1)). This framework enables the use of standardised formulations when describing methods, presenting results, and discussing findings.

In this HTA, NOMA employees will collaborate with clinical experts from the health authorities and patient representatives, recruited via "*Nye metoder"* and the Norwegian Cancer Society ("*Kreftforeningen"* in Norwegian).

Project group	
Project manager:	Ida-Kristin Ørjasæter Elvsaas (IKØE), clinical effectiveness and safety, organisational implications, and patient perspectives
Internal project group:	Geir Smedslund (GS), clinical effectiveness and safety Vida Hamidi (VH), health economics Fawaz Tariq Chandhry (FTC), health economics Gunn Eva Næss (GEN), information retreival
External clinical experts:	Recruited through "*Nye metoder"*
Patient representatives:	Representatives from the Norwegian Cancer Society (*Kreftforeningen*)
Head of unit:	Carolin Hagen

Declared conflicts of interest

All project members, experts, and reviewers have completed a declaration of interest according to NOMA policies. No conflicts of interest were reported.

NOMA is solely responsible for the content of this protocol.

Acknowledgement of AI tool usage in this HTA protocol

As part of NOMA's commitment to innovation and efficiency in preparing HTAs, we have utilised AI tools to support our work. In this HTA protocol, we employed ChatDMP, an AI-powered language model developed for use at NOMA, to enhance the clarity, consistency, and readability of several sections of the document. However, all suggestions from ChatDMP were approved by our team.

Glossary and abbreviations

Term/abbreviation	Explanation
AJCC	American Joint Committee on cancer
ASA	Acetylsalicylic acid
CI	Confidence interval
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CRC	Colorectal cancer
DFS	Disease-free survival
FDA	Food and drug administration
Gene alteration	A inherited or acquired change or mutation in the DNA sequence of a gene that may affect its function.
GRADE	Grading of recommendations assessment, development, and evaluation
HTA	Health technology assessment
HTAi	Health technology assessment international
ICER	Incremental cost-effectiveness ratio
ICTRP	International clinical trials registry platform
INAHTA	International network of agencies for health technology assessment
MCID	Minimal clinically important difference
MD	Mean difference
MeSH	Medical subject headings
Mutation (somatic)	A genetic alteration acquired by a cell that can be passed to the progeny of the mutated cell during cell division
NGS	Next generation sequencing
NOMA	Norwegian Medical products agency
NOK	Norwegian kroner
NSAIDs	Non-steroidal anti-inflammatory drugs
OS	Overall survival
PICO	Population, intervention, comparator, outcome
PI3K	Phosphatidylinositol-3-kinase: A family of enzymes involved in intracellular signaling pathways that regulate cell growth, survival, metabolism, and proliferation. Dysregulation of this pathway is commonly associated with cancer development.
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha: A gene encoding the catalytic subunit of PI3K, which is frequently mutated in various cancers and plays a role in tumour progression.
PIK3R1	Phosphoinositide-3-kinase regulatory subunit 1: A gene encoding a regulatory subunit of PI3K, which helps control PI3K activity. Alterations in this gene can contribute to cancer development.
PTEN	Phosphatase and tensin homolog deleted on chromosome 10: A tumour suppressor gene that negatively regulates the PI3K pathway by dephosphorylating phosphatidylinositol substrates. Loss or mutation of PTEN is associated with cancer progression.
QALYs	Quality-adjusted life years

QoL	Quality of life
RCTs	Randomised controlled trials
RevMan	Review manager (computer software)
RoB 2	Risk of bias 2
SMD	Standarised mean difference
Somatic gene alteration	A change or mutation in the DNA sequence of a gene that occurs in somatic (non-reproductive) cells and may affect its function. Somatic gene alterations are acquired rather than inherited and are often associated with diseases, including cancer, where they may influence tumour behaviour and response to treatment.
TTR	Time to recurrence

1. Introduction

1.1 Description of the disease and patient population

Colorectal cancer (CRC), which includes cancers of the colon and rectum, arises from the accumulation of genetic and epigenetic alterations in oncogenes and tumour-suppressor genes, including those involved in DNA repair (2-4). Environmental factors, sedentary lifestyles, and dietary habits further increase the risk (5). These genetic changes disrupt the balance between cell proliferation and death, leading to the formation of polyps in the intestinal mucosa and, eventually, cancer (2;3).

CRC symptoms vary depending on tumour location and are often unrecognised in early stages because they tend to be non-specific or mild (2). Common symptoms include abdominal pain, changes in bowel habits, and blood in the stool (6). Advanced tumours may obstruct the intestinal lumen, causing complications such as ileus (intestinal obstruction) and, in severe cases, bowel wall perforation (6).

CRC represents a substantial global health burden, with approximately 1.9 million new cases diagnosed annually (7). Norway has one of the highest incidence rates of CRC worldwide, with 4,995 new cases registered in 2024, comprising 3,509 cases of colon cancer and 1,486 of rectal cancer (8). This makes CRC the most common cancer in Norway when considering both genders combined (8). By the end of 2024, 43,049 individuals in Norway were living with CRC, accounting for over 12% of all cancer cases (8). In the same year, CRC caused 1,534 deaths, representing over 13% of all cancer-related mortality in Norway (8).

In Norwegian clinical practice, the management of stage I–III CRC is primarily curative, with surgery as the mainstay of treatment (9). Neoadjuvant radiotherapy is selectively used for rectal cancer, and risk-adapted adjuvant chemotherapy is applied for stage II and III disease (9). In 2024, approximately 1,782 colon cancer patients with stage II–III underwent surgery, with or without adjuvant chemotherapy, in Norway (10). For rectal cancer patients with stage I–III, 807 underwent surgery, also with or without adjuvant chemotherapy (10). The estimated five-year relative survival after surgery for colon cancer patients (stage I–III) was 89.7% in 2024 (8). Similarly, for rectal cancer patients (stage I–III), the estimated five-year relative survival was 92.2% (8).

Although surgery is intended as a curative treatment for CRC, approximately one-fifth of patients with CRC stages I–III experience disease recurrence, according to a nationwide Danish cohort study (11). This underscores the need for effective adjuvant treatment strategies. Adjuvant therapy aims to eliminate residual tumour cells, including occult micrometastases, in patients with no visible disease following curative surgery (12).

1.2 Adjuvant acetylsalicylic acid treatment

Several non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid (ASA), have been investigated both as prophylactic agents and as treatments for cancer (13). This is likely due to the role of chronic inflammation as a key factor in the development and progression of CRC (14).

ASA is widely used for managing fever and pain, as thrombosis prophylaxis in cardiovascular diseases, and as an acute intervention for myocardial infarction or ischaemic stroke (15). ASA treatment is generally well-tolerated, with the most common side effects being an increased risk of bleeding and gastrointestinal symptoms such as nausea, vomiting, and diarrhoea (16;17). Regular use of ASA may also elevate the risk of stomach bleeding and gastric ulcers (16). However, this risk is reduced with enteric-coated tablets, which dissolve in the intestine rather than the stomach (16). The costs associated with daily low-dose ASA treatment are relatively low (16;17).

ASA's mechanism of action involves the irreversible inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), which blocks the formation of prostaglandins and thromboxanes involved in pain, inflammation, and thrombosis (15). Furthermore, COX-2 is frequently overexpressed in various cancers, including CRC, and is associated with poorer survival outcomes (18). Certain

prostaglandins produced via COX activity are also implicated in activating the phosphatidylinositol-3-kinase (PI3K) signalling pathway, which regulates key cellular processes such as proliferation and survival (19), a pathway commonly deregulated in CRC.

PI3K is a family of lipid kinases composed of a regulatory subunit (phosphoinositide-3-kinase regulatory subunit 1: *PIK3R1*) and a catalytic subunit (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha: *PIK3CA*). It plays a central role in cell signalling by phosphorylating phosphatidylinositol, a key component of the cell membrane, to produce lipid signalling intermediates that promote cell growth, survival, and metabolism (3). Phosphatase and tensin homolog deleted on chromosome 10 (*PTEN*) acts as a tumour suppressor by counteracting PI3K signalling through the dephosphorylation of these lipid intermediates, thereby maintaining cellular balance (20).

Deregulation of the PI3K pathway is a common feature of CRC and is often associated with mutations in *PIK3CA*, *PIK3R1*, and/or loss of function in *PTEN*, as well as other molecular alterations, such as amplification of upstream receptors (20;21). These gene alterations contribute to CRC pathogenesis and are associated with clinical characteristics, prognosis, and treatment response (3;21;22). Mutations in *PIK3CA*, particularly in exons 9 and 20, result in constitutive activation of the PI3K pathway, driving tumour growth and survival (22). Conversely, alterations in *PIK3R1* and loss of function in *PTEN* typically result in reduced regulation of the PI3K pathway, further contributing to tumour progression and resistance to treatment (23;24).

The incidences of alterations in PI3K pathway genes in CRC tumours vary between studies, with one Nordic trial reporting that 37% of tumours had PI3K pathway alterations (18). Gene alterations in *PIK3CA* have been found in 7% to 25% of CRC tumours (3;18;20;22), while *PTEN* gene alterations or loss of function have been found to occur in approximately 9% to 35% (20;25). *PIK3R1* gene alterations have been observed in approximately 6%, and loss of *PIK3R1* function in between 18% and 28% (21).

Given the role of the PI3K pathway in CRC pathogenesis and its association with treatment response, alterations in *PIK3CA*, *PIK3R1* and *PTEN* have been proposed as potential predictive biomarkers for adjuvant ASA treatment in individuals who have undergone surgery for colon cancer (stages II–III) or rectal cancer (stages I–III) (18). This is particularly relevant, as adjuvant ASA treatment for all CRC patients has not demonstrated a statistically significant reduction in CRC recurrence compared to placebo (26). Genotyping of *PIK3CA*, *PIK3R1*, and *PTEN* may therefore be important for personalising adjuvant ASA treatment in postoperative CRC patients (18), helping to avoid overtreatment in those unlikely to benefit and preventing unnecessary harm.

1.3 Companion diagnostics

A companion diagnostic is an in vitro medical device that provides critical information for the safe and effective use of a corresponding drug or biological product (27). These diagnostics help identify patients most likely to benefit from a specific therapy, those at heightened risk of severe side effects, or those requiring treatment adjustments to enhance safety and efficacy (27). In cancer treatment, companion diagnostics are important, as they enable the precise identification of genomic alterations that drive tumour progression and influence therapeutic responses.

While adjuvant ASA treatment for CRC patients with alterations in *PIK3CA*, *PIK3R1*, and *PTEN* has been proposed (18), no companion diagnostic tests specifically targeting these gene alterations to guide targeted therapy in CRC are currently available (28). Instead, these markers are included in broader next-generation sequencing (NGS) panels, which are used to identify mutations in genes such as *PIK3CA*, *PIK3R1*, and *PTEN* with high accuracy in cancer clinical diagnostics and research.

Despite its advantages, implementing NGS in clinical settings poses several challenges. Establishing the necessary infrastructure – including investment and maintenance costs, adequate data capacity, storage, and trained personnel with expertise in data analysis and interpretation – is essential (29;30).

In Norway, according to "*Sykehusinnkjøp HF"*, there are currently no national agreements covering tests for all three genes—*PIK3CA*, *PIK3R1*, and *PTEN* (31). Although hospitals have implemented a

range of NGS panels for routine diagnostics, expanded testing in the CRC patient group will likely require substantial scale-up and increased capacity.

1.4 Why is it important to do this HTA

Despite the clinical need, there have been limited major advances in adjuvant treatment options for CRC over the past two decades. At the same time, the cost of new cancer medicines continues to increase. This has led to growing interest in optimising the use of existing, affordable drugs in patient groups most likely to benefit (12;32). ASA is a potential example of such a repurposed treatment (32).

A 2025 systematic review suggests that adjuvant ASA treatment in postoperative CRC improves disease-free survival and reduces recurrence risk in patients with PI3K alterations, without causing serious adverse events (33). Molecular testing is therefore central to the treatment strategy, as it identifies patients most likely to benefit from ASA and helps avoid unnecessary treatment and potential adverse effects in those unlikely to benefit.

In Norway, routine testing for *PIK3CA*, *PIK3R1*, and/or *PTEN* alterations in CRC stage I-III tumours is currently not performed. Similarly, ASA treatment is not established as an adjuvant CRC treatment for patients with these gene alterations (31). To the best of our knowledge, no cost-effectiveness studies have been conducted on ASA treatment in postoperative nonmetastatic CRC patients with *PIK3CA*, *PIK3R1*, and *PTEN* gene alterations.

Therefore, the relevant decision problem is not whether ASA should be used after CRC surgery, but whether routine molecular testing followed by targeted ASA treatment in mutation-positive stage I–III CRC patients represents a clinically meaningful and cost-effective strategy in Norway. Such an evaluation would help determine whether the benefits, risks, and costs of testing and targeted treatment justify implementation in routine post-surgical CRC care.

1.5 Aim

The aim of this HTA is to address the prioritisation criteria of health benefit, severity, and resource use.

We will:

- Evaluate the clinical effectiveness and safety of adjuvant ASA treatment in patients who have undergone surgery for CRC stages I–III and have *PIK3CA*, *PIK3R1*, and/or *PTEN* gene alterations in their tumours.
- Conduct a combined health economic evaluation of molecular testing for *PIK3CA*, *PIK3R1*, and *PTEN* tumour gene alterations in CRC patients stages I–III, followed by adjuvant ASA treatment.
- Describe organisational aspects related to the implementation of adjuvant ASA treatment for CRC patients stages I–III with *PIK3CA*, *PIK3R1*, and *PTEN* gene alterations in tumours.

Additionally, the patient perspective, informed by written input from members of the Norwegian Cancer Society, will be summarised thematically and included in the HTA.

1.5.1 Limitations

Due to the lack of specifically targeted methods (companion diagnostics) for detecting gene alterations relevant to adjuvant ASA treatment, the absence of a gold standard for identifying gene alterations in *PIK3CA*, *PIK3R1*, and/or *PTEN*, and previous research findings indicating that the quality of similar studies on detecting *PIK3CA* in breast cancer was too low to assess sensitivity and specificity (30), it is not feasible to perform sensitivity and specificity analyses for different molecular testing methods.

However, clinical experts have suggested that NGS is the most relevant approach for detecting these gene alterations. NGS will therefore be used as the molecular test method in the health economic evaluation.

1.6 External experts

When initiating the project, we recruited clinical experts appointed by "*Nye metoder*," with expertise in pathology and oncology, to serve as medical consultants. Patient representatives from the Norwegian Cancer Society were recruited to provide input on patient perspectives.

The expert group's role is to provide information about the patient population, intervention, comparators, and relevant outcomes, thereby aiding in the definition of the inclusion criteria. They also play a key role in describing clinical practice, patient pathways, and resource use within the healthcare sector. Additionally, they may assist in interpreting the HTA results and contribute to the discussion section of the final report. Patient representatives will provide insights into the lived experiences of the patient group. Both clinical experts and patient representatives will be allowed to provide input on the protocol and relevant chapters of the final report draft.

2. Clinical effectiveness and safety – methods

We will conduct a systematic review to determine the clinical effectiveness and safety of adjuvant ASA treatment in patients with *PIK3CA*, *PIK3R1*, and *PTEN* tumour gene alterations who have undergone surgery for colon cancer (stage II-III) or rectal cancer (stage I-III).

The review will follow the methods recommended by the Norwegian Institute of Public Health's guide *"Slik oppsummerer vi forskning"* (1) and the Cochrane Handbook (34).

2.1 Selection criteria for clinical effectiveness and safety

The inclusion criteria for the assessment of clinical effectiveness and safety of adjuvant ASA treatment in patients with *PIK3CA*, *PIK3R1*, and *PTEN* tumour gene alterations who have undergone surgery for colon cancer (stage II-III) or rectal cancer (stage I-III) are described below:

Population	Individuals >18 years of age who have undergone surgery for colon cancer (stage II–III) and/or rectal cancer (stage I–III) with somatic gene alterations in *PIK3CA*, *PIK3R1*, and/or *PTEN*. Cancer stages assessed according to the criteria in the AJCC [American Joint Committee on Cancer] Cancer Staging Manual (35), Dukes' staging system (36), or similar
Intervention	ASA treatment, any dosage and duration
Comparator	Placebo

Outcome	- Overall survival (OS)
	- Disease-free survival (DFS)
	- Time to recurrence (TTR)
	- Treatment discontinuation / cessation
	- Quality of life (QoL)
	- Adverse events / adverse effects / safety
	  o Fatal
	  o Non-fatal

Study design	Randomised controlled trials (RCTs), protocols of RCTs
Publication year	No limit
Land/context	No limit
Language	English, Scandinavian, Persian
Other	None

With the inclusion of randomised trials, we will be able to suggest causality, depending on the trials' risk of systematic bias.

2.1.1 Exclusion criteria

We exclude the following types of studies and publications:

- Systematic reviews, HTAs, reviews
- Observational studies
- Commentary, editorials, conference abstracts, doctoral theses

2.2 Literature search

2.2.1 Search in databases

The information retrieval specialist (GEN) will develop a search strategy in collaboration with the team and, following best practices in the field (37;38), conduct the literature searches. Search tactics will be tailored to suit the unique interface of each electronic bibliographic database. For the population and intervention concepts, the search strategy will include both keywords and controlled vocabulary, such as MeSH (Medical Subject Headings) from the National Library of Medicine. Boolean operators "OR" and "AND" will be used to combine search terms and concepts, respectively. We will not limit the search by language or publication year. A second information retrieval specialist will proofread the search strategies before the literature searches are conducted. Documentation of the search process and results will be included in the HTA report.

The search is scheduled to conclude in February 2026 and will include searches in the following databases:

- Medline (platform)
- Embase (platform)
- Epistemonicos (platform)
- INAHTA (platform)
- Clinical trials.gov (study registry)
- WHO ICTRP (study registry)

The search results from bibliographic databases and study registries will be exported to the reference management tool EndNote (39). Duplicates will be removed using a standardised, semi-automated method (40). The unique records will then be uploaded to the online reference screening tool Rayyan (41) for relevance assessment against the inclusion and exclusion criteria.

2.2.2 Search in other sources

It may be relevant to review the reference lists of relevant identified systematic reviews. Additionally, consulting clinical experts involved in this HTA may help identify any relevant publications.

2.3 Selection of studies

The reviewers (GS, GEN, IKØE) will independently screen titles and abstracts from the literature search against the inclusion criteria using the online screening tool Rayyan (41). We will pilot the inclusion criteria on the first 25 studies, to ensure that the reviewers have a common understanding of the inclusion criteria.

We will retrieve the relevant studies in full text, and the same reviewers will independently assess the full-text articles against the inclusion criteria. Disagreements regarding inclusion and exclusion will be addressed through discussions after a new review of the studies. If the disagreement persists, another project team member will be consulted to help reach a consensus.

A list of publications excluded after full-text review will be included in the report’s appendix

2.4 Assessment of risk of bias

We will assess the risk of bias in the included studies. We will use Cochrane's Risk of Bias 2 (RoB v2) (42;43). We may use Cochrane’s web-based Review Manager (RevMan) software to summarise and visualise the assessments (44).

The assessments will be conducted at the study outcome level. The five domains included in RoB v2 (42) are: 1) bias arising from the randomisation process; 2) bias due to deviations from intended interventions; 3) bias due to missing outcome data; 4) bias in the measurement of the outcome; and 5) bias in the selection of the reported result.

Two reviewers (GS, IKØE) will independently conduct the risk of bias assessments. Disagreements regarding the assessments will be resolved through discussion following a re-evaluation of the studies. If the disagreement persists, a third team member will be consulted to help reach a consensus.

2.5 Data extraction

One reviewer (IKØE) will extract data from the included studies, while a second reviewer (GS) will cross-check the extracted data against the relevant publications to identify any potential errors. Any disagreements will be resolved by consensus or by consulting a third project member.

We plan to use a custom-made Excel sheet for the data extraction process. Additionally, we may utilise an AI tool called Google NotebookLM (45) to support this process. Google NotebookLM is an online AI tool based on Gemini 2.0, designed to assist users in interacting with documents (45).

If needed, e.g., if the data are unclear or missing, we will contact the authors to request additional information for use in our HTA. Furthermore, if multiple publications are linked to the same study, they will be treated as a single study and reported together with all associated references. Table 1 presents an overview of the data to be extracted from the included studies.

Table 1. Data to be extracted from the included studies

Concerning	Information to be extracted
The study	Authors, publication year, study design, total duration of study, number of study centres and locations, setting, funding, clinical identification number
The participants	Number of participants in each group, age range, sex, ethnicity, cancer type and stage, biomarker test, gene alterations
The intervention	ASA treatment, dose/dosage, duration
The comparator	Placebo, type
The outcomes	Definitions of outcomes, means, medians, standard deviations, or confidence intervals at baseline and post-intervention and follow-up assessment(s), contextual information if provided (see **Feil! Fant ikke referansekilden.** for details)

2.6 Analysis

We will group the studies and results according to the outcome measures. Most analyses and calculations will be performed using the web-based RevMan software (44).

2.6.1 Effect estimates

We will estimate hazard ratios (HR) for time-to-event outcomes and risk ratios (RR) for dichotomous outcomes, each reported with corresponding 95% confidence intervals (CI).

For continuous outcomes measured with similar measurement methods, we will calculate the mean difference (MD) with 95% CI. For outcomes measured by different measurement methods, we will calculate the standardised mean difference (SMD) with 95% CI. The SMD corresponds to Hedges' *g*, which is often interpreted as follows: small effect size = 0.2-0.5, medium effect size = 0.5-0.8, and large effect size > 0.8 (46).

Where possible, we will also calculate estimates of effect with 95% CI for studies that have not provided these themselves, using RevMan (44). We will calculate effect estimates for relevant outcomes reported in the included studies, even if meta-analyses are not possible.

When conducting meta-analyses, we will use relative effect estimates directly from the included studies. If the studies report data in other ways, e.g., in figures or graphs, we will extract the available data either manually or using software tools, such as PlotDigitizer (47), a free, web-based tool for

extracting data from 2D plots, bar graphs, scatter plots, and other types of visualisations. Where possible, we will use the standard methods available in RevMan (44) to impute relative effect estimates for inclusion in meta-analyses.

Statistically adjusted effect estimates are preferable to unadjusted effect estimates (such as the number of events). Adjustments are needed to deal with both precision and systematic bias. In RCTs, adjustment related to precision adjustment for baseline values includes clustering effects (e.g., if the unit of randomisation is different from the unit used to randomise), and other design-based adjustments (e.g., adjustment for a variable used in the randomisation process).

2.6.2 Meta-analysis

Where feasible, we will compile the results of the included studies in meta-analyses. This requires that the studies are sufficiently homogeneous in terms of study design, participants, intervention, comparator(s), outcome measures, and any confounding factors adjusted for in the analyses. When meta-analyses are not feasible, we will present the results narratively.

As we cannot anticipate identical populations, interventions and outcomes across the included studies, we will use a random effects model in the meta-analyses. The random-effects model assumes that each study's sample is drawn from different populations. In other words, we assume that there is not one true effect, but rather that each study can present slightly varying effects, from which we calculate an average effect. Generally, this gives somewhat wider confidence intervals compared to the fixed-effect model. If the studies report both adjusted and unadjusted effect estimates, we will use the adjusted estimates. We will conduct pairwise meta-analyses and present forest plots and pooled effect estimates for each meta-analysis.

We will assess potential sources of statistical heterogeneity in study outcomes by examining the confidence intervals (CIs) and calculating Chi^2 and I^2 using RevMan (44). Wide CIs may indicate variability in effect estimates across studies, with poor overlap of CIs generally suggesting heterogeneity (48). The Chi^2 test evaluates whether observed differences in results are greater than would be expected by chance (48). A significant p-value (<0.05) suggests heterogeneity, but this test is sensitive to the number and/or the size of studies (48). The I^2 statistic quantifies the percentage of variability in effect estimates attributable to heterogeneity rather than chance. I^2 values between 0–40% are unlikely to be important, 30–60% may indicate moderate heterogeneity, 50–90% may indicate substantial heterogeneity, and 75–100% suggest considerable heterogeneity (48). If a high degree of heterogeneity is identified, we may conduct subgroup analyses based on population type (i.e., cancer stage) or setting. Additionally, we may perform sensitivity analyses by excluding studies with a high risk of bias, or small or underpowered studies. Finally, we will report CIs, Chi^2, p-values, and I^2 for heterogeneity and discuss how heterogeneity affects the interpretation of our findings.

2.6.3 Narrative analysis

We will calculate and present effect estimates for relevant outcomes reported in the included studies, even if meta-analyses cannot be performed. In such cases, we will summarise and explain the effect estimates, for example, using forest plots without an 'overall effect estimate' and providing additional context in the supporting text.

2.7 Assessment of certainty of evidence

By 'certainty of the evidence,' we refer to the extent to which the research results reflect the 'true' or 'real' effect of the intervention(s). Another way to put it is how thoroughly documented the research results are. We will assess the certainty of the evidence using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach (49) and possibly the digital tool GRADEpro (50). While the degree of confidence is continuous, it is divided into four categories in GRADE for practical purposes: high, medium, low, and very low certainty, as shown in Table 2.

Table 2. The GRADE categories of the degree of confidence in the evidence

GRADE level	Symbol	Definition
High certainty	⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty	⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty	⊕⊕◯◯	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty	⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

To determine the level of confidence in the evidence, we will first consider the study design and then consider five criteria: 1) risk of systematic bias (risk of bias); 2) degree of consistency of the results between studies (inconsistency); 3) indirectness; 4) sparse data/precision of data (imprecision); and 5) publication bias.

Two reviewers will assess the certainty of the evidence for the following outcomes: overall survival; disease-free survival; time to recurrence; treatment discontinuation; quality of life; adverse events (fatal/non-fatal).

Any disagreements will be resolved by consensus or by consulting a third project member.

3. Health economy - methods

Priority setting in the Norwegian healthcare system is based on three principles: health benefit, resource use, and severity (51). Health technology assessments, and particularly health economic evaluations, are essential for quantifying these criteria.

To evaluate the health economic consequences of adjuvant treatment with ASA in patients with colorectal cancer who have *PIK3CA*, *PIK3R1*, and *PTEN* alterations compared to current clinical practice, we will conduct a model-based cost-utility analysis. This analysis will include the evaluation of molecular testing and treatment in a combined model. A scenario analysis will compare biomarker-guided treatment with ASA treatment without biomarker testing to estimate the incremental value of biomarker testing and patient selection.

This analysis will be implemented in TreeAge Pro 2026 to estimate and compare the costs and health outcomes associated with the treatment alternatives in the Norwegian context. The model will adopt a lifetime time-horizon with health effects expressed in terms of quality-adjusted life years (QALYs).

We will use Norwegian treatment guidelines and expert advice to inform model assumptions and structure, where appropriate. Efficacy estimates and adverse event data will be derived from our systematic literature review. When available, we will use Norwegian epidemiological data; in the absence of such data, we will rely on the best available transferable data. A separate search will be conducted to identify the overall survival data and the utility weights required to calculate quality-adjusted life years in the model. Utility weights, preferably measured by EQ-5D, will be collected to represent quality of life across different disease stages and for relevant adverse events.

We will calculate costs in Norwegian kroner (NOK) from an extended healthcare sector perspective. This approach includes all relevant healthcare costs in the Norwegian setting but excludes broader societal costs, such as productivity losses. This perspective aligns with priorities established within a fixed healthcare budget, as outlined in the Priority-setting White Paper (51). Norwegian unit prices will be applied to estimate these costs. Both costs and health outcomes will be discounted at 4% per year as recommended by the Norwegian guidelines (52).

The results of the model will be expressed as incremental cost-effectiveness ratios (ICERs), where the numerator captures the difference in costs between the interventions, and the denominator reflects the difference in effects between them. All uncertain input parameters will be modelled as probability distributions to reflect their associated uncertainty. Sensitivity and scenario analyses will be performed to assess the robustness of the results. In addition, to quantify the severity principle, we will calculate the absolute shortfall for individuals with colorectal cancer who have *PIK3CA*, *PIK3R1*, and *PTEN* alterations treated with standard of care.

4. Organisational aspects – methods

We will describe the organisational aspects and consequences associated with the potential introduction of ASA treatment in patients with *PIK3CA*, *PIK3R1*, and *PTEN* tumour gene alterations who have undergone surgery for colon cancer (stage II-III) or rectal cancer (stage I-III). The development of a national implementation strategy is outside the scope of this project. The assessment will address the implications that implementation of the intervention may have for the healthcare system (53).

Our approach to assessing organisational aspects will follow the procedure outlined in the Norwegian Institute of Public Health's methodology manual (1). We will consult the expert group to identify and explore relevant organisational issues. NOMA will prepare a questionnaire to support the collection of relevant information, which will be used during the information-gathering process. In addition, relevant publications, guidelines, and recommendations will be used as supplementary sources of information and as a basis for discussion in this chapter.

Information on the potential public funding of ASA for the CRC population will be collected from the Directorate of Health. In addition, the Norwegian Hospital Procurement Trust will be asked to map the existing NGS infrastructure and the panels currently in use in Norwegian hospitals.

The limitations of our approach should be noted. We will not conduct a systematic literature review, and the assessment will rely primarily on input from the clinical experts recruited to the project. However, as the clinical experts represent the Norwegian health trusts, we assume that they have sufficient knowledge of relevant organisational aspects of the health service to provide pertinent input on the topic. This input, together with existing guidelines, recommendations and current practice in Norway, is expected to provide an adequate basis for the Decision Forum's consideration of the organisational aspects of the potential introduction of ASA treatment for patients with *PIK3CA*, *PIK3R1*, and *PTEN* tumour gene alterations who have undergone surgery for colon cancer (stage II-III) or rectal cancer (stage I-III).

One project team member (IKØE) will be responsible for overseeing the information-gathering process and drafting the chapter, in collaboration with the other team members and the expert group.

5. Patient experiences – methods

Patients, caregivers, family members, and friends can offer unique perspectives on their experiences, attitudes, preferences, beliefs, and expectations regarding health, illness, service delivery, and therapies (53). These insights can contribute to an HTA by informing both the PICO framework and the lived experiences of the disease.

We will primarily employ our Norwegian adaptation of the HTAi questionnaire for patient input (54) to collect information. The questionnaire will be distributed to patient representatives from the Norwegian Cancer Society for completion on behalf of their members and summarised thematically.

It is important to acknowledge the limitations of this approach in capturing patient experiences. Specifically, it does not include a systematic review of the literature on patient experiences, nor does it constitute primary research. Consequently, the results will be limited to insights provided by members of the Norwegian Cancer Society, which will be discussed in the context of published literature.

One project team member (IKØE) will be responsible for the information-gathering process and drafting the chapter, with input from the other team members, the expert group, and patient representatives.

6. Deliverables and publication

6.1 Delivery

The approved protocol will be published on www.dmp.no and www.nyemetoder.no. It will also be made available in the INAHTA database.

The primary deliverable from this work will be an HTA report prepared following the methods outlined in the Norwegian Institute of Public Health's methodology manual (1) and using NOMA's template for HTAs. The report is primarily intended for the Ordering Forum and Decision Forum for "*Nye Metoder*", but it should also be accessible to a broader audience. The report will be written in English and published on www.dmp.no and www.nyemetoder.no. Additionally, we are open to publishing the entire report or parts of its content as one or more articles in scientific journals.

6.2 Peer review of the protocol and report

Protocol

The protocol will be reviewed internally by reviewers at the unit for health technology assessment of medical devices and by the external expert group before receiving final approval from the head of unit.

Report

After the final HTA report has been reviewed and approved by the external expert group and internal reviewers, we will consider submitting it for external peer review. Following this process, the HTA report will be submitted to the head of unit for final approval.

6.3 Time frame

Start date: In the first meeting with the appointed clinical experts on **22.04.2026**, we determined the research question and inclusion criteria.

End date: **19.04.2027**, proposed date for submission to the Ordering Forum

Of note, a specific timetable is available for internal staff in the project's project folder.

6.3.1 Delays and unforeseen project developments

If circumstances arise that pose a risk that the delivery deadline cannot be met, such as unforeseen long-term absences among project members or other circumstances, one or more of the following will be appropriate:

- Increased staffing within the agreed framework of man-months.
- Replacing project employees in the event of absence or illness.
- Restrictions on inclusion criteria (by agreement with the commissioner).
- Extension of the delivery deadline (by agreement with the commissioner).

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